Facultad de Ciencias

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Metal-Catalyzed C(sp^2)–H and C(sp^3)–H Functionalization Reactions: Nitration of Anilines and γ-Carbonylation of Amino Acid Derivatives

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“The meeting of two personalities is like the contact of two chemical substances: if there is any reaction, both are transformed.”

C. G. Jung

To my family, specially to my parents.

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Standard Abbreviations and Acronyms

Standard Abbreviations and Acronyms

The standard abbreviations and acronyms found in the Guideliness for Authors, *J. Org. Chem*. **2013**, were used along with the followings:

Å: angstrom

AQ: 8-aminoquinoline

^{i}**AmONO**: *iso*-amyl nitrite

Atm: atmosphere

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Boc: *tert*-butyloxycarbonyl

Bpin: pinacolatoboryl

BQ: 1,4-benzoquinone

Bz: benzyl

CAN: cerium ammonium nitrate

cat.: catalytic

(*S,S*)-Chiraphos: (2*S*,3*S*)-(-)-bis(diphenylphosphino)butane

conc.: concentrated

cy: cyclohexane, cyclohexyl

dba: dibenzylideneacetone

D: diffusion coefficient

DCE: dichloroethane

DCM: dichloromethane

DFT: density functional theory

DG: directing group

DMA: dimethylacetamide

DMAP: 4-dimethylaminopyridine

DMEDA: *N,N*-dimethylethylenediamine

DMF: *N,N*-dimethylformamide

DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMSO: dimethyl sulfoxide

DOSY: Diffusion-Ordered NMR Spectroscopy

Duroquinone: 2,3,5,6-tetramethyl-1,4-benzoquinone

E: electrophile

EDC·HCl: *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride

EDG: electron-donating group

***ee**:* enantiomeric excess

EM: elemental mass

equiv.: equivalent(s)

EWG: electron-withdrawing group

[F^+]: *N*-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate

FG: functional group

Fesulphos: (R_p)-2-(*tert*-Butylthio)-1-(diphenylphosphino)ferrocene

Fmoc: 9-fluorenylmethoxycarbonyl

g: gaseous

GC: gas chromatography

h: hour(s)

HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol

HOBt·H_2O: 1-hydroxybenzotriazole hydrate

HOMO: Highest Occupied Molecular Orbital

HPLC: high-performance liquid chromatography

HRMS: high-resolution mass spectroscopy

Hz: Hertz

IR: Infrared spectroscopy

J: coupling constant

Josiphos:(*S*)-1-{(*RP*)-2-[Bis[3,5-bis(trifluoromethyl)phenyl]phosphino]-ferrocenyl}ethyldicyclohexylphosphine

K: kelvin degree(s)

LUMO: Lowest Unoccupied Molecular Orbital

LHMDS: lithium bis(trimethylsilyl)amide

M: molar

m: meta

Mandyphos: (R_P,R'_P)-1,1′-Bis{bis[3,5-bis(trifluoromethyl)phenyl]phosphino}-2,2′-bis[(*S*)-α-(dimethylamino)benzyl]ferrocene

Meduphos: (-)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene

MIA: 2-methoxyiminoacetyl

MS: molecular sieves

MW: molecular weight

Ms: mesylate (from methanesulfonic acid)

NBS: *N*-bromosuccinimide

NCS: *N*-chlorosuccinimide

NIS: *N*-iodosuccinimide

NMP: *N*-methyl-2-pyrrolidone

NMR: nuclear magnetic resonance

NOE: nuclear overhauser effect

o: ortho

OTf: trifluoromethanesulfonate

p: para

PA: picolinamide

PG: protecting group

Phth: phthlamide

PIP: 2-(pyridine-2-yl)-isopropylamine

Py: pyridine

rt: room temperature

SET: single electron transfer

-SO_2Ns: (4-nitrophenyl)sulfonyl

-SO_2Py: (2-pyridyl)sulfonyl

-SO_2Pyr: (2-pyrimidyl)sulfonyl

-SO_2Tol: (4-methylphenyll)sulfonyl

T: temperature

t: time

Taniaphos: (R_P)-1-[(*R*)-α-(Dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrocene

TBHP: *tert*-butyl hydroperoxide

TBME: methyl *tert*-butyl ether

TBN: *tert*-butyl nitrite

Tc: thiophene-2-carboxylate

TCP: 1,2,3-trichloropropane

TDA: tris-(3,6-dioxaheptyl)amine

TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy

TFA: trifluoroacetic acid

TFEol: 2,2,2-trifluoroethan-1-ol

THF: tetrahydrofuran

TMEDA: *N,N,N′,N′*-tetramethylethylenediamine

TNT: trinitrotoluene

ρ: density

η: viscosity

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Chapter 1:

Research focus

1. Research focus

Chemical synthesis has reached a maturity level such that compounds of amazing structural complexity can be readily synthesized.[1] However, despite such enormous achievements, inefficiencies in the synthetic processes often limit the real application of these molecules towards societal problems. The concept of *atom economy* was created to emphasize the importance of this inefficiency.[2] Consequently, one of the main goals of modern Organic Chemistry is to increase efficiency and minimize chemical waste according to the *Green Chemistry* principles.[3] Within this context, the development of tactics enabling control over all aspects of reaction selectivity in synthetic transformations (this can be regio-, chemo- or stereoselectivity) stands at the forefront of Organic Synthesis and homogeneous catalysis.

The metal-catalyzed direct C–H functionalization, namely, the direct transformation of a non-activated C–H bond into a C–C or C–X bond, has the potential to dramatically simplify the synthesis of complex organic molecules, allowing the introduction of functional diversity and structural complexity into organic compounds with high chemical efficiency and low environmental impact (Figure 1.1).[4,5] It allows the utilization of less expensive and more readily available starting

[1] K. C. Nicolaou, J. S. Chen, *Classics in Total Synthesis III: Further Targets, Strategies, Methods*; Wiley-VCH, Weinheim, **2011**.

[2] a) B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, *34*, 259. b) B. M. Trost, *Science* **1991**, *254*, 1471.

[3] a) J. H. Clark, *Green Chem*. **2006**, *8*, 17. b) P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, **2000**. c) J. H. Clark. *Green Chem.* **1999**, *1*, 1. See also: d) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695.

[4] For general reviews on metal-catalyzed C–H functionalization reactions, see: a) J. J. Mousseau, A. B. Charette, *Acc. Chem. Res.* **2013**, *46*, 412. b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879. c) K. M. Engle, T. –S. Mei, M. Wasa, J. –Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788. d) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740. e) A. L. Dick, M. S. Sanford, *Tetrahedron*, **2006**, *62*, 2439. f) J. A. Labinger, J. E. Bercaw, *Nature*, **2002**, *417*, 507. g) W. D. Jones, *Science*, **2000**, *287*, 1942. See also the June 2012 issue of *Acc. Chem. Res,* the April 2011 issue of *Chem. Rev.*, and the March 2011 and February 2010 issues of *Chem. Soc. Rev.*

materials compared to the classical cross-coupling approaches that rely on pre-existing functional groups such as halogen or pseudo-halogen derivatives.

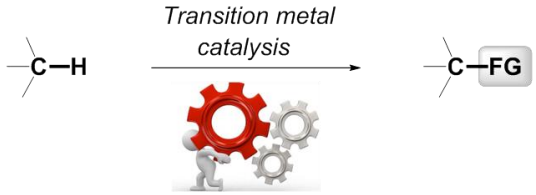


Figure 1.1

1.1. Precedents of our research group

1.1.1. Metal-catalyzed C=C and C=N functionalization using directing groups

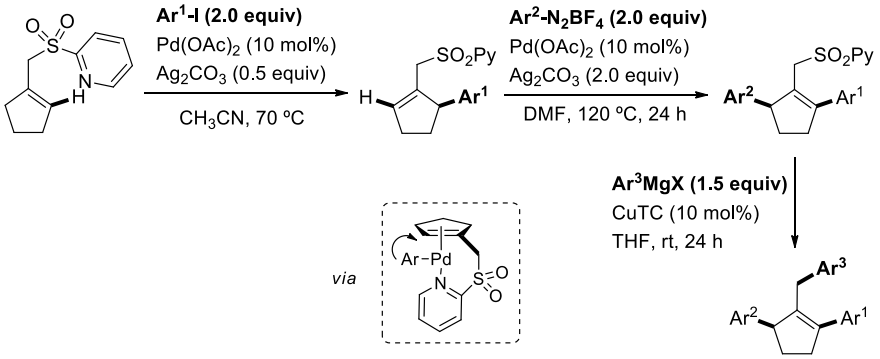
In 2004 our research group started a new research line oriented to explore the potential of heteroarylsulfonyl groups [especially the (2-pyridyl)sulfonyl group] as *temporary auxiliary directing groups* in transition metal-catalyzed reactions.[6] It was rapidly found that this group promoted a dual effect: 1) it usually enhanced the reactivity and selectivity of the process by means of pre-association of the metal-catalyst to the *N*-pyridyl unit, and 2) after the reaction, the sulfonyl group could be easily removed under mild reaction conditions.

For selected textbooks on C–H functionalization reactions, see: h) J. Dupont, M. Pfeffer, *Palladacycles*, Wiley-VCH, Weinheim, **2008**. i) G. Dyker, *Handbook of C–H Transformations,* Volumes 1 and 2, Wiley-VCH, Weinheim, **2005**.

[5] For reviews on the application of C–H functionalization to the total synthesis of complex molecules, see: a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. b) D. Y. –K. Chen, S. W. Youn, *Chem. Eur. J.* **2012**, *18*, 9452. c) L. McMurray, F. O´Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885. d) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976. e) K. Gouda, D. Sames, *Science*, **2006**, *312*, 67.

[6] For a recent review on the use of temporary directing groups in organometallic reactions, see: G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.

Along this line, a pioneering example was the development of a chelation-assisted, transition metal-catalyzed protocol for the sequential multi-arylation of cyclic allyl sulfones. As shown in Scheme 1.1, the metal-coordinating ability of the 2-pyridyl group on the sulfone promoted the otherwise difficult intermolecular Heck mono-arylation and di-arylation of trisubstituted alkenes, as well as the copper-catalyzed allylic arylation with Grignard reagents.[7,8] The role of the metal coordinating (2-pyridyl)sulfonyl group was crucial to accomplish this goal, as proven by the fact that the corresponding tosyl or phenyl sulfonyl derivatives were inert in this reaction, even under harsher reaction conditions.



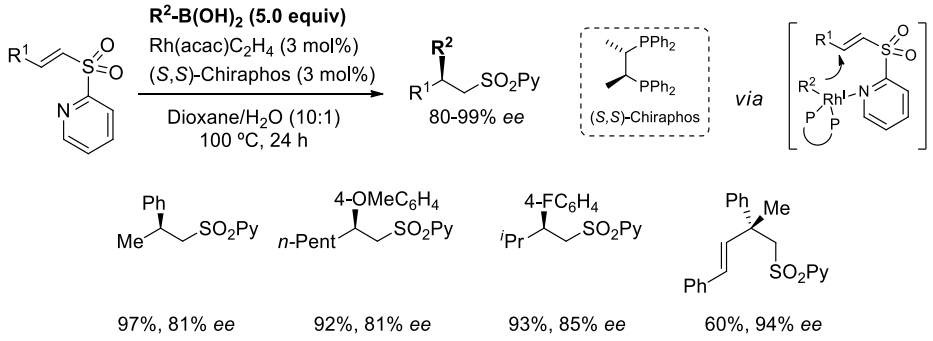
Scheme 1.1

On the other hand, combining the *N*-(2-pyridyl)sulfonyl moiety as directing group with a chiral organometallic catalyst has led to the development of new asymmetric catalytic processes. For example, our research group described in 2004 the first catalytic protocol for the enantioselective conjugated addition of carbon nucleophiles

[7] T. Llamas, R. Gómez Arrayás, J. C. Carretero, *Adv. Synth. Catal*. **2004**, *346*, 1.

[8] For the Heck arylation of α,β-insaturated 2-(*N*,*N*-dimethylamino)phenyl sulfones, see: a) I. Alonso, M. Alcami, P. Mauleón, J. C. Carretero, *Chem. Eur. J.* **2006**, *12*, 4576. b) P. Mauleón, A. A. Nuñez, I. Alonso, J. C. Carretero, *Chem. Eur. J.* **2003**, *9*, 1511. c) P. Mauleón, I. Alonso, J. C. Carretero, *Angew. Chem. Int. Ed.* **2001**, *40*, 1291. For the reaction of *N*-(2-pyridyl)sulfonyl azabenzonorbornadienes with cuprates, see: d) R. Gómez Arrayás, S. Cabrera, J. C. Carretero, *Synthesis* **2006**, 1205. e) R. Gómez Arrayás, S. Cabrera, J. C. Carretero, *Org. Lett*. **2005**, *7*, 219.

to α,β-unsaturated sulfones.[9] The (2-pyridyl)sulfonyl group was essential to attain high reactivity and enantioselectivity in the Rh-catalyzed conjugate addition of boronic acids to vinyl sulfones using (*S*,*S*)-Chiraphos as the optimal chiral ligand, providing the Michael addition products with excellent yields and high enantiomeric excesses (76-92% *ee*, Scheme 1.2).[10] The method could be applied to both *E*- and *Z*-substrates and tolerated a wide variety of substituents at the β-position to the sulfone, as well as in the boronic acid. The elimination of the (2-pyridyl)sulfonyl group through a Julia-Kocienski-type reaction opened a new pathway to optically active alkenes substituted at the allylic position. This methodology was also extended to the construction of stereogenic quaternary centers through the enantioselective addition of boronic acids to α,β-unsaturated-β,β-di-substituted-(2-pyridyl)sulfones (88-99% *ee*).[11]



Scheme 1.2

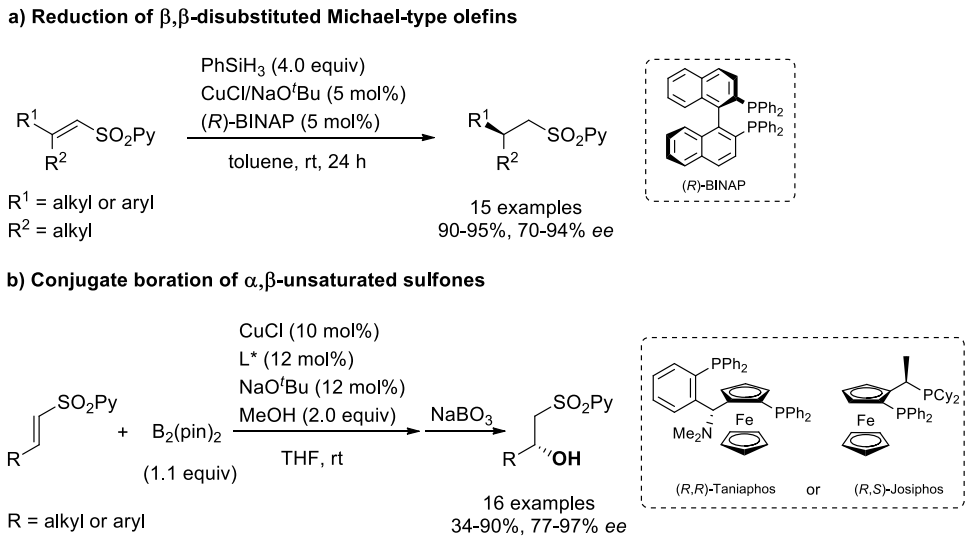
Our group has also been pioneer on incorporating vinyl sulfones into the arsenal of electrophiles that efficiently participate in the enantioselective Cu-catalyzed conjugate addition of β,β-di-substituted Michael-type acceptor olefins (Scheme

[9] a) P. Mauleón, I. Alonso, M. Rodríguez Rivero, J. C. Carretero, *J. Org. Chem.* **2007**, *72,* 9924. b) P. Mauleón, J. C. Carretero, *Org. Lett.* **2004**, *6*, 3195.

[10] For a recent review on rhodium-catalyzed conjugate addition reactions, see: H. J. Edwards, J. D. Hargrave, S. D. Penrose, C. G. Frost, *Chem. Soc. Rev.* **2010**, *39*, 2093.

[11] P. Mauleón, J. C. Carretero, *Chem. Commun.* **2005**, 4961.

1.3a)[12,13] and the asymmetric Cu-catalyzed conjugate boration of α,β-unsaturated systems (Scheme 1.3b).[14] In the latter case, *in situ* oxidation of the resulting chiral β-boronates affords the corresponding β-hydroxysulfones in good yields and high enantioselectivities.



Scheme 1.3

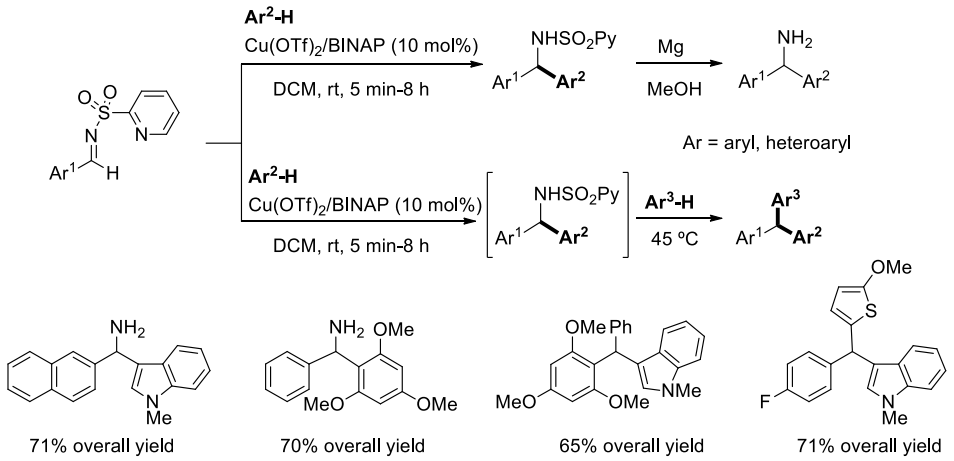
This concept has also been extended to reactions of coordinating *N*-(heteroaryl)sulfonyl imines. These new electrophiles proved to be extremely reactive compared to traditional *N*-tosyl imines. An example of this strategy has been the development of a very general protocol for the synthesis of diaryl amines and dialkyl amines based on the Friedel-Crafts reaction of *N*-(2-pyridyl)sulfonyl imines

[12] T. Llamas, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2007**, *46,* 3329.

[13] For a review on the topic, see: a) S. Rendler, M. Oestreich, *Angew. Chem. Int. Ed*. **2007**, *46*, 498. For selected texbooks, see: b) A. Córdova, *Catalytic Asymmetric Conjugate Reactions*, Wiley-VCH, Weinheim, **2010**. c) P. G. Andersson, I. J. Munslow, *Modern Reduction Methods*, Wiley-VCH, Weinheim, **2008**.

[14] A. L. Moure, R. Gómez Arrayás, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6701.

with electron-rich aromatic and heteroaromatic compounds (Scheme 1.4).[15] In this reaction, the presence of the coordinating group was essential for stopping the process in the mono-addition product, whereas the analogue *N*-Ts or *N*-aryl imines provided exclusively the double addition derivatives under identical conditions.[16] The deprotection of the sulfonamides could cleanly be achieved under mild conditions. This method also allowed an *in situ* second electrophilic aromatic substitution with a different nucleophilic arene species (Ar^3–H) promoted by the same Lewis acid catalyst. This sequential addition of two arenes to the *N*-(2-pyridyl)sulfonyl imine constituted the first one-pot synthesis of unsymmetrical triarylmethanes. DFT theoretical studies of the second Friedel-Crafts reaction suggests that the different reactivity of the *N*-(2-pyridyl)sulfonyl imines could be attributed to their coordinating mode to the metal, in comparison to the typical *N*-tosyl derivatives.[17]



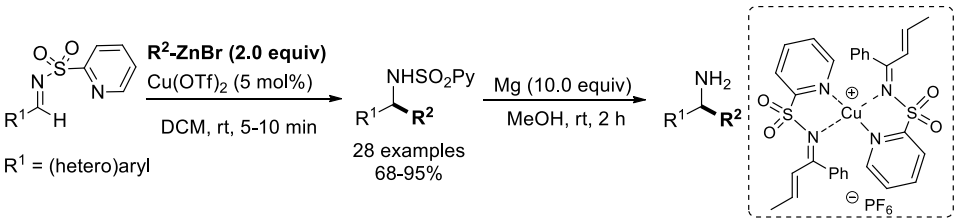
Scheme 1.4

[15] J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed*. **2006**, *45*, 629.

[16] For selected examples, see: a) I. Alonso, J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *J. Org. Chem.* **2008**, *73*, 6401. b) B. Ke, Y. Qin, Q. He, Z. Huang, F. Wang, *Tetrahedron Lett*. **2005**, *46*, 1751. c) J. Hao, S. Taktak, K. Aikawa, Y. Yusa, M. Hatano, K. Mikami, *Synlett* **2001**, 1443.

[17] I. Alonso, J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *J. Org. Chem*. **2008**, *73*, 6401.

The same strategy has been applied to the development of the first general protocol for the Cu-catalyzed direct addition of alkylzinc halides to imines (Scheme 1.5).[18,19] The *N*,*N*-bidentate character of the (2-pyridyl)sulfonyl imines with respect to metal coordination, demonstrated by X-ray crystallography of the Cu^{I}-complex of a chalcone derivative, was suggested as the origin of the exceptional reactivity displayed by these substrates. The deprotection of the sulfonamide group took place under mild reductive conditions, compatible with many sensitive functional groups.



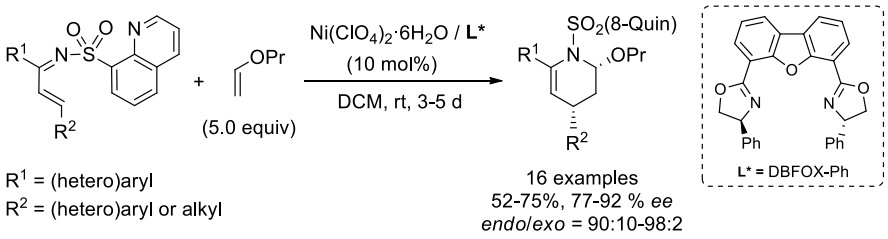
Scheme 1.5

This strategy could also be exploited in cycloaddition reactions. For example, the high reactivity that the *N*-(8-quinolyl)sulfonyl protecting group confers to α,β-unsaturated imines allowed the development of the first example of a catalytic asymmetric inverse-electron-demand Diels-Alder reaction of *N*-sulfonyl-1-aza-1,3-dienes.[20] Up to the date, this reaction required harsh reaction conditions, which hampered the development of asymmetric versions. The combination of $Ni(ClO_4)_2.6H_2O$ as catalyst and DBFOX-Ph as ligand (both in 10 mol%) enabled the reaction of this *N*-sulfonyl azadienes with alkyl vinyl ethers to afford the corresponding piperidine derivatives in good yields, excellent *endo*-selectivities and high enantioselectivities (Scheme 1.6).

[18] J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed*. **2007**, *46*, 9257.

[19] Our group has also described the copper-catalyzed asymmetric conjugate addition of dialkyl zinc reagents to α,β-insaturated ketimines (80-90% yield, 70-80% *ee*), see: J. Esquivias, R. Gómez Arrayás, J. C. Carretero *J. Org. Chem.* **2005**, *68*, 8120.

[20] J. Esquivias, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480.



Scheme 1.6

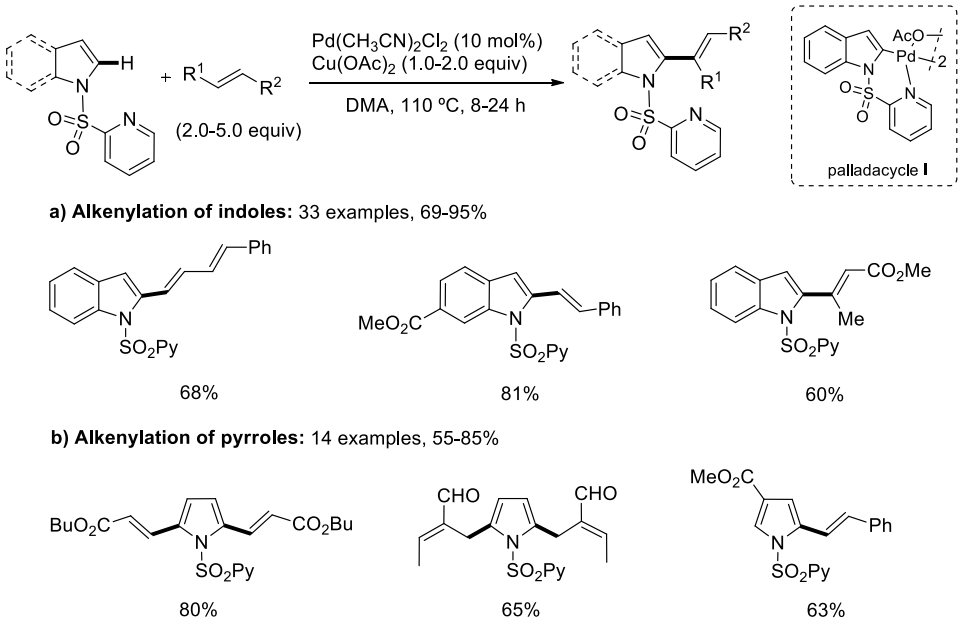
1.1.2. Metal-catalyzed C–H functionalization using directing groups

More recently, our group has demonstrated that the activating effect of the (2-pyridyl)sulfonyl unit (and related sulfur-based groups) in metal-mediated reactions can be applied to the challenging Pd-catalyzed C–H activation processes.[21] This concept was first investigated in the Pd^{II}-catalyzed regioselective C2-alkenylation of *N*-(2-pyridyl)sulfonyl indoles and pyrroles.[22] The coordinating ability of the *N*-(2-pyridyl)sulfonyl group was critical for inducing C–H activation with complete regiocontrol at the less favoured C2-position, likely through formation of palladacycle **I**. For instance, the *N*-Ts protected indole led to less than 20% conversion under identical conditions, whereas the low conversion and regiocontrol observed for the (3-pyridyl)sulfonyl group strongly suggests that the high selectivity observed for the (2-pyridy)sulfonyl is likely to originate from its metal-coordination ability through the formation of palladacycle **I**. The reaction combines not only high reactivity and complete regiocontrol but also with substrate/reagent versatility. (Scheme 1.7a). This method was also applicable to the functionalization of pyrroles. Monosubstituted, disubstituted, as well as unsymmetrical 2,5-disubstituted pyrroles could be obtained by small variations in the reaction conditions (Scheme 1.7b). Removal of the *N*-(2-pyridyl)sulfonyl group from indoles and pyrroles was readily

[21] For an overview on the use of sulfonyl coordinating substrates in metal-catalyzed reactions, see: J. Hernández, A. García-Rubia, B. Urones, R. Gómez Arrayás, J. C. Carretero, *Phosphorus, Sulfur and Silicon* **2011**, *186*, 1019.

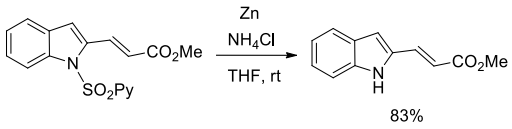
[22] a) A. García-Rubia, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed*. **2009**, *48*, 6511.

achieved by reductive cleavage with Zn to give 2-alkenyl-substituted heteroarenes.[23,24]

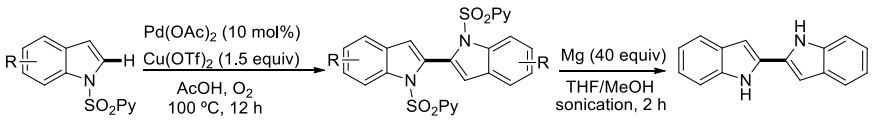


Scheme 1.7

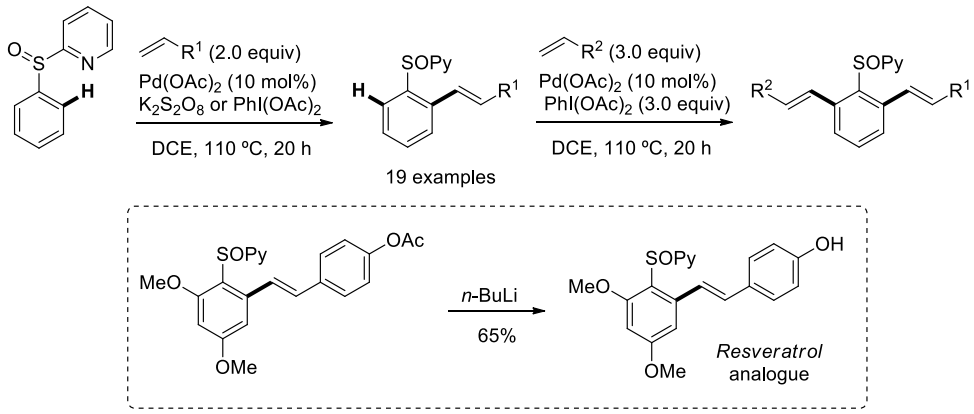
[23] For the reductive removal of the (2-pyridyl)sulfonyl directing group, see Scheme bellow:



[24] This *N*-(2-pyridyl)-sulfonyl directing strategy has also been extended to the development of a protocol for the intermolecular cross dehydrogenative homocoupling of indoles, providing 2,2´-biindoles, which are structural units frequently found in pharmaceuticals and functional materials (see Scheme bellow): A. García-Rubia, B. Urones, R. Gómez Arrayás, J. C. Carretero, *Chem. Eur. J.* **2010**, *16*, 9676.



This sulfur-mediated directing group strategy has not only been limited to the (2-pyridyl)sulfonyl moiety. For example, we have also reported a practical Pd^{II}-catalyzed *ortho* C–H alkenylation of arenes assisted by the (2-pyridyl)-sulfoxide,[25] a group that can be readily removed or transformed into other functionalities such a thiol group, thereby offering an additional handle to introduce diversity and complexity in the final product. Electron-deficient alkenes and styrene-type olefins serve as efficient coupling partners, providing access to either mono-alkenylated or asymmetrically di-*ortho*-alkenylated products (through a sequential double C–H alkenylation) in good yields and high selectivities. The practical utility of this sequence is illustrated in the formal synthesis of *Resveratrol*, a naturally occurring product of the *Phytoalexin* family with important biological activities including anticancer properties (Scheme 1.8).[26]



Scheme 1.8

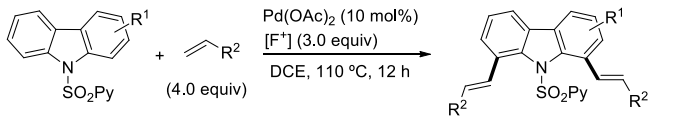
[25] a) J. A. Romero-Revilla, A. García-Rubia, R. Gómez Arrayás, M. A. Fernández-Ibáñez, J. C. Carretero, *J. Org. Chem.* **2011**, *76*, 9525. b) A. García-Rubia, M. A. Fernández-Ibáñez, R. Gómez Arrayás, J. C. Carretero, *Chem. Eur. J.* **2011**, *17*, 3567.

[26] B. Sun, J. Hoshino, K. Jermihov, L. Marler, J. M. Pezzuto, A. D. Mesecar, M. Cushman, *Bioorg. Med. Chem.* **2010**, *17*, 3567.

More recently, we have applied the directing ability of the *N*-(2-pyridyl)sulfonyl group to the Pd^{II}-catalyzed *ortho* C–H alkenylation of *N*-alkyl aniline derivatives with a variety of electron-poor alkenes (Scheme 1.9).[27] Remarkably, excellent catalyst performance was attained with especially challenging (low reactive) aniline substrates, including those bearing a strong electron-withdrawing substituent (CF_3, CO_2R) or those *ortho*-substituted. Because of an unprecedented flexibility with regard to the tether length, not only anilines, but also benzylamines (one-carbon longer tether), phenethylamines (two-carbon longer tether) and γ-arylpropylamines (three-carbon longer tether) were suitable substrates. In this reaction, the use of a strong oxidant (*N*-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate) [F^+] was crucial to accomplish the corresponding *ortho*-olefinated products in high yields (typically ≥ 70%) with complete regiocontrol and excellent levels of (*E*)-diastereoselectivity.[28] The mild reductive *N*-sulfonyl deprotection of the resulting products, which resulted compatible with the labile conjugated olefin moiety, enabled the construction of a diversity of medicinally relevant architectures, such as indoles, isoindoles or tetrahydroisoquinolines. [29]

[27] A. García-Rubia, B. Urones, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2011**, *50*, 1.

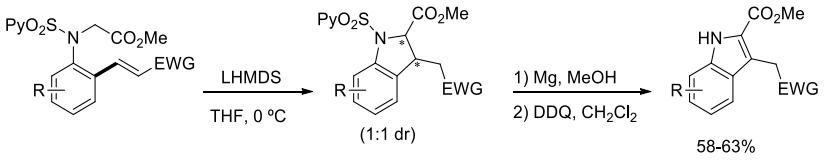
[28] This *N*-(2-pyridyl)sulfonyl directing strategy has recently been extended to the development of a protocol for C(sp^2)–H olefination of carbazoles, leading to regiocontrolled C1/C8 di-olefinated products: B. Urones, R. Gómez Arrayás, J. C. Carretero, *Org. Lett.* **2013**, *15*, 1120.



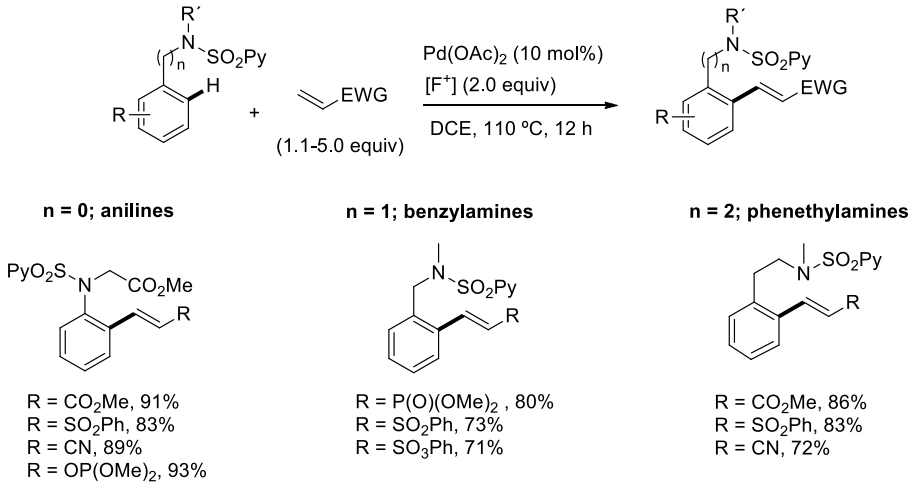
48-91%

R^2 = -CO_2Alkyl, -SO_2Ph, -*p*-$NO_2C_6H_4$

[29] A simple three-step transformation of the olefination products into functionalized indoles was devised, see Scheme bellow.



58-63%



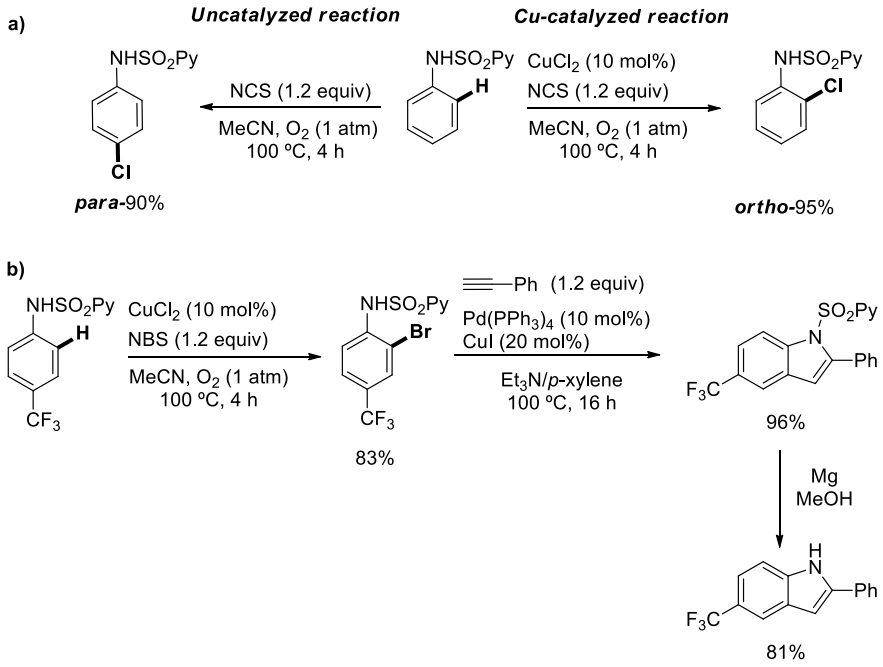
Scheme 1.9

Finally, two other projects belonging to different Ph.D. Theses, that were being carried out in our group during the course of this research, deserve special mention because both served as point of departure for two of the projects developed within the framework of this Thesis.

Compared to noble metals, first-row transition metals are easily available, far less expensive and biologically tolerated. As a consequence, their use as catalysts attracts increasing attention, especially for C–H activation reactions.[30] Moreover, oxidative coupling reactions with these metals under O_2 are extremely attractive from both academic and industrial standpoints. Within this context, we have recently demonstrated that the (2-pyridyl)sulfonyl directed C–H activation is compatible with copper catalysis, thereby benefitting from different mechanistic pathways (e.g., radical-mediated) which results in novel patterns of reactivity or selectivity. For example, in 2013, our research group reported a practical and highly regioselective

[30] For a review on copper-catalyzed C–H functionalization reactions, see: a) X. –X. Guo, D. –W. Gu, Z. Wu, W. Zhang, *Chem. Rev.* **2015**, *115*, 1622. For a review on cobalt-catalyzed C–H functionalization reactions, see: b) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208.

N-(heteroaryl)sulfonyl-directed Cu-catalyzed aerobic *ortho*-C–H halogenation of aniline derivatives with *N*-halogen-succinimide derivatives (mainly chlorination with NCS and bromination with NBS).[31] This new strategy provides complementary *ortho*-regioselectivity to that of the classical electrophilic aromatic halogenation pathway (Scheme 1.10a).The reaction is operationally simple and typically shows excellent mono-substitution and large functional group tolerance. Additionally, the easy *N*-protecting group removal under mild conditions (Mg turnings, MeOH, sonication), enabled the development of useful synthetic applications (Scheme 1.10b).



Scheme 1.10

[31] For the Cu-catalyzed halogenation of protected anilines, see: a) B. Urones, A. M. Martínez, N. Rodríguez, R. Gómez Arrayás, J. C. Carretero, *Chem. Commun.* **2013**, *49*, 11044. For a more recent Cu-catalyzed amination of protected anilines, see: A. M. Martínez, N. Rodríguez, R. Gómez Arrayás, J. C. Carretero, *Chem. Commun.* **2014**, *50*, 2801.

Compared to the C(sp^2)–H activation, the directed functionalization of the less reactive C(sp^3)–H bond remains underdeveloped. In this context, the direct functionalization of α-amino acid derivatives has captured the focus of much research effort due to their wide range significance. We have also become attracted by this exciting area and recently demonstrated that the -SO_2Py auxiliary group can be applied to the efficient γ-remote activation of C(sp^3)–H bonds of aliphatic side chain in amino acids.[32] Thus, a variety of *N*-(2-pyridyl)sulfonyl-protected amino acid derivatives react with iodoarenes (1.5-5.0 equiv) in the presence of $Pd(OAc)_2$ (10 mol%) and AgOAc (1.5 equiv) as oxidant in HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) (1.0 M) as solvent[33] to provide the corresponding γ-C–H arylation products in synthetically useful yields (Scheme 1.11). The process occurs without racemization at the C_α center when starting from chiral non-racemic α-amino acid derivatives. A bimetallic Pd^{II} γ-metalated **complex A** has been isolated and characterized, highlighting the key role played by the -SO_2Py unit.[34] This complex was shown to be catalytically competent in the reaction. Notably, dipeptides were also suitable substrates affording the corresponding monoarylated products in acceptable to good yields, which represent the first C(sp^3)–H arylation of dipeptides reported in the literature.[35]

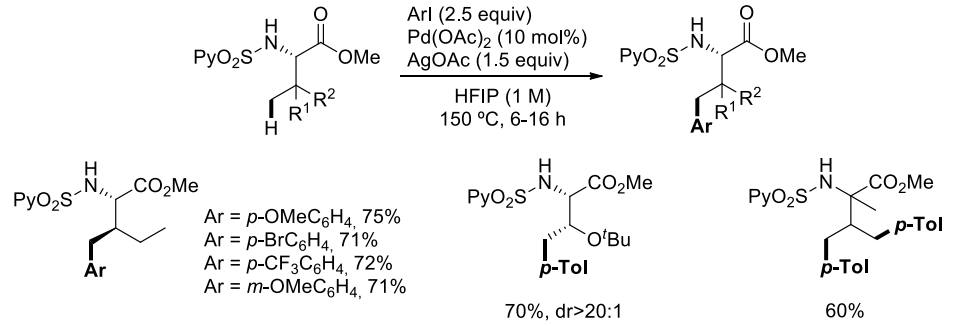
[32] a) N. Rodríguez, J. A. Romero-Revilla, M. A. Fernández-Ibáñez, J. C. Carretero, *Chem. Sci.* **2013**, *4*, 175. For a detailed mechanistic study on this reaction, see: b) A. Poveda, I. Alonso, M. A. Fernández-Ibáñez, *Chem. Sci.* **2014**, *5*, 3873.

[33] For selected examples on the use of HFIP in C–H activation processes, see: a) W. R. Gutekunst, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 19076. b) M. Ochiai, K. Miyamoto, T. Kaneaki, S. Hayashi, W. Nakanishi, *Science* **2011***, 332*, 448.

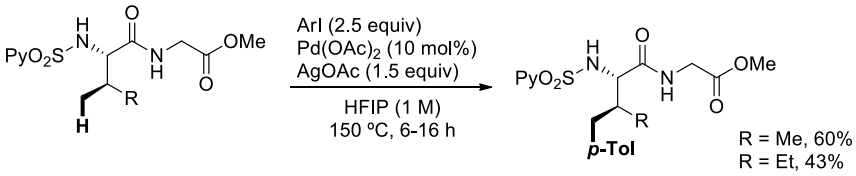
[34] A complete structural characterization of this complex is provided in Chapter 3.

[35] For a selected publication on the C(sp^2)–H arylation of peptides, see: J. Ruiz-Rodríguez, F. Albericio, R. Lavilla, *Chem. Eur. J.* **2010**, *16*, 1124.

a) γ-C(sp^3)–H arylation of amino acid derivatives



b) γ-C(sp^3)–H arylation of dipeptides



Scheme 1.11

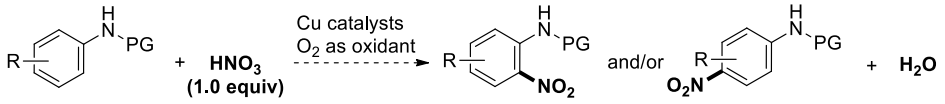
1.2. General research objective and Thesis organization

The development of tactics for reactivity and selectivity control in the field of metal-catalysis stands at the forefront of the Synthetic Organic Chemistry, as it allows higher transformation efficiency. This is particularly stringent for C–H functionalization reactions owing to the ubiquitous nature of C–H bonds in organic substances and their inherent low reactivity. The use of directing groups to overcome issues of reactivity and selectivity has received significant attention. However, despite huge advances, a number of challenges, especially concerning the reactivity, selectivity and cost-effectiveness, still remain to be solved.

Our group has introduced the (2-pyridyl)sulfonyl moiety (and related sulfur-based groups) as a new type of removable metal-coordinating directing group in metal-catalyzed reactions of unsaturated sulfones and *N*-sulfonyl imines. Very recently, this activating effect was also extended to challenging C–H functionalization reactions: the Pd-catalyzed regioselective C(sp^2)–H alkenylation of *N*-(2-pyridyl)sulfonyl indoles, pyrroles and carbazoles, the Cu-catalyzed C(sp^2)–H halogenation of *N*-(2-pyridyl)sulfonyl anilines and the challenging remote γ-C(sp^3)–H arylation of *N*-(2-pyridyl)sulfonyl amino acid derivatives.

The enhanced reactivity and regiocontrol provided by these coordinating heteroarylsulfonyl groups opens up very appealing scenarios for developing novel methodologies in C–H activation processes that could significantly contribute to the state of the art in the field. Therefore, ***the aim of this Thesis is to explore and evaluate the extension of this "N-heteroarylsulfonyl activation" to other type of functionalization of both aromatic [C(sp^2)–H] and amino acid derivatives [C(sp^3)–H] systems.*** These general objectives have been organized into two chapters covering more specific goals as follows. It should be noted that each dissertation chapter contains a specific introduction that places the research into context with relevant literature precedents followed by research focus and specific research objectives.

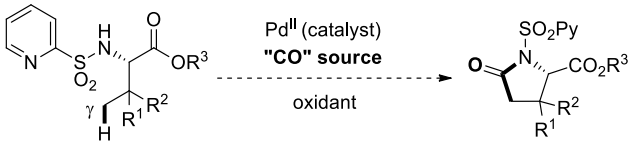
Chapter 2 presents the development of an operationally simple, amenable to scale-up, Cu-catalyzed procedure for the selective nitration of a wide range of differently *N*-protected *para*-substituted and *ortho*-substituted aniline derivatives by using one equivalent of HNO_3 and molecular oxygen as terminal oxidant, which produces water as the only stoichiometric by-product. The use of inexpensive, safe and easy to handle copper salts and the possibility of employing MeCN or mixtures of MeCN/H_2O as solvent, also contributed to the eco-friendliness character of this new protocol.



R = EWG, EDG, halogens

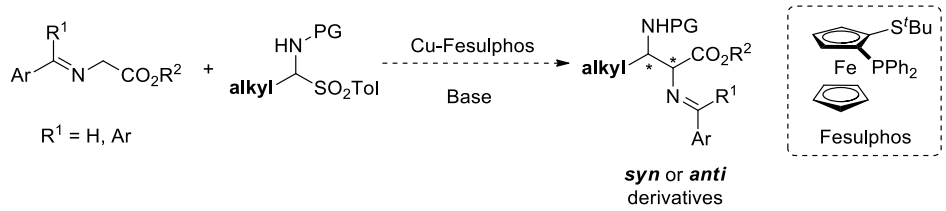
PG = sulfonamides, amides, carbamates, ureas

Chapter 3 describes a general procedure for the selective Pd-catalyzed functionalization of unactivated γ-C(sp^3)–H bonds of aliphatic amines and α-amino acids that strongly relies on the use of *N*-(2-pyridyl)sulfonyl directing group. The use of substoichiometric amounts of $Mo(CO)_6$ as a safe and practical source of carbon monoxide was also crucial for attaining high levels of reactivity. In addition to exploiting the synthetic potential of this transformation, a special focus has been placed on the study of the reaction mechanism, both experimentally and computationally, in order to gain understanding of the factors that control the reactivity and selectivity of catalytic species.



Chapter 4 compiles the general experimental procedures and characterization data of all the products synthesized in Chapters 2 and 3.

Annex I provides a brief overview of a collateral research project centered on a different field: asymmetric catalysis. It describes a practical Cu^{I}-Fesulphos-catalyzed Mannich-type reaction of glycinate Schiff bases with aliphatic, enolizable imines generated *in situ* from α-amido sulfones to afford chiral, non-racemic β-alkyl-α,β-diamino acid derivatives with high levels of regio- and enantioselectivity.



R^1 = H, Ar

syn or ***anti*** derivatives

1.2. Objetivos general y estructura de la presente Memoria

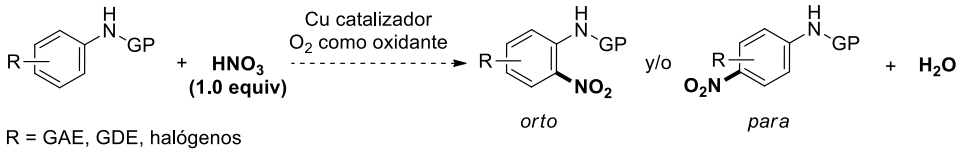
El desarrollo de nuevas estrategias catalíticas que permitan ampliar la reactividad y selectividad de las reacciones orgánicas constituye una de las áreas dominantes de la síntesis orgánica moderna. En particular, los procesos de funcionalización directa C–H catalizada por metales de transición presenta un enorme interés -tanto a nivel académico como aplicado- debido al carácter ubicuo de los enlaces C–H y su inherente baja reactividad, así como la eficiencia potencial de esta estrategia al no requerir la prefuncionalización del sustrato. En este contexto, la aproximación más común es la utilización de grupos directores, que mediante su coordinación con el átomo metálico permiten la activación de enlaces C–H, incluso en posiciones remotas.

En los últimos años, nuestro grupo investigador ha desarrollado el grupo (2-piridil)sulfonilo (y especies de azufre relacionadas) como un nuevo tipo de grupo director coordinante y fácilmente eliminable. En nuestros primeros estudios, este grupo se empleó como una herramienta sintética para la activación de vinilsulfonas y *N*-sulfonil iminas. Más recientemente, nuestro grupo investigador ha demostrado que el auxiliar (2-piridil)sulfonilo también es efectivo en procesos de activación C–H, tales como la alquenilación regioselectiva C(sp^2)–H de indoles, pirroles y carbazoles catalizada por paladio, la halogenación C(sp^2)–H de anilinas catalizada por cobre y la arilación de enlaces C(sp^3)–H en la posición remota γ de derivados amino ácidos catalizada por paladio.

La elevada reactividad y buen control de la selectividad observada en estos primeros estudios de funcionalización C–H constituyen los precedentes inmediatos de esta Tesis Doctoral e invitan a extender el empleo de grupos heteroarilsulfonilo coordinantes a otras reacciones de funcionalización C–H de gran interés sintético, tanto procesos de funcionalización aromática [C(sp^2)–H] como alifática [C(sp^3)–H]. Estos objetivos generales han sido organizados en dos capítulos que se explicarán más detalladamente a continuación. Cabe destacar que cada uno de los capítulos consta de una introducción propia que permite al lector

contextualizar, mediante un exhaustivo análisis de los precedentes bibliográficos, el tema de investigación desarrollado.

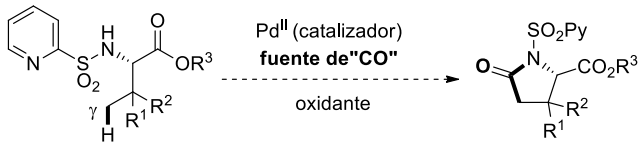
En el **Capítulo 2** se describe un nuevo método general y escalable para la nitración selectiva de derivados de anilina catalizado por cobre. Entre las grandes ventajas prácticas de este procedimiento se encuentra la utilización de un único equivalente de HNO_3 y oxígeno como oxidante, que suponen condiciones de reacción de mínimo impacto ambiental al generar agua como subproducto.



R = GAE, GDE, halógenos

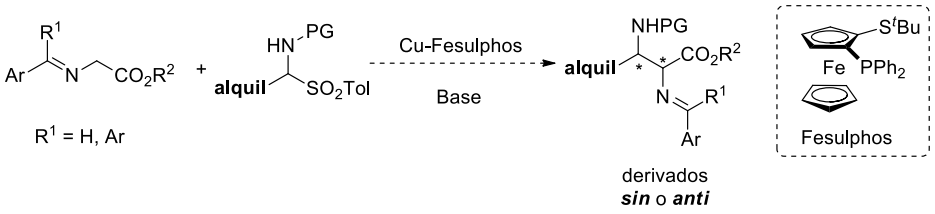
GP = sulfonamidas, amidas, carbamatos, ureas

En el **Capítulo 3** se presenta un método eficaz para la γ-C(sp^3)–H ciclación carbonilativa de derivados de aminoácidos catalizada por paladio. La utilización del grupo (2-piridil)sulfonilo resultó crucial para alcanzar buenos niveles de reactividad y selectividad. Cabe destacar igualmente el empleo subestequiométrico de $Mo(CO)_6$ como alternativa al uso de CO gas. Este capítulo también recoge el potencial sintético de la reacción y diversos estudios mecanísticos (experimentales y cálculos computacionales).



En el **Capítulo 4** se recogen los procedimientos experimentales generales así como la caracterización completa de todos los productos sintetizados en los capítulos 2 y 3.

En el **Anexo I** se describe brevemente un proyecto de investigación colateral en el ámbito de la catálisis asimétrica. En particular, se recogen los resultados de una nueva versión asimétrica catalizada por cobre de la reacción de Mannich entre glicinatos e iminas alifáticas, estas últimas generadas *in situ* a partir de α-amido sulfonas.



Chapter 2:

Copper-Catalyzed Mild Nitration of Protected Anilines

2. Copper-catalyzed mild nitration of protected anilines

2.1. Importance of nitroarenes

Nitroarenes are currently relevant and appealing motifs among industrial chemicals. Additionally, due to the great versatility of the nitro group, mainly as source of nitrogen functionalities, nitroarenes are also essential building blocks for synthetic chemists operating within both academic and industrial settings.

Nitroaromatic compounds are organic molecules that present at least one nitro group ($-NO_2$) attached to an aromatic ring. Two oxygen atoms bonded to a partially positive nitrogen atom provide the nitro group a very strong electron-withdrawing character. When an aromatic ring presents a nitro moiety in its structure, the nitro group is able to delocalize π-electrons of the ring to balance its charge deficiency. Consequently, a partial charge is generated in the molecule providing nitro substituted arenes a unique reactivity in organic syntheses.[36]

Although the vast majority of biologically active nitroarenes are manufactured products, some bacteria, fungi and plants can produce them.[37] For example, members of gems *Streptomyces* are well-known to produce nitroarene-based antibiotics, of which *Chloramphenicol* is perhaps the best known (Figure 2.1). Other nitro-containing antibiotics produced by *Streptomyces* include *Orinocin* (a

[36] For a general review, see: a) M. Makosza, *Chem. Eur. J.* **2014**, *20*, 5536. For general selected texbooks, see: b) J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, **2001**. c) N. Ono, *The Nitro group in Organic Synthesis,* Wiley-VCH, New York, **2001**.

[37] For a general review on pharmaceutical properties of nitro compounds, see: a) K.-S- Ju, R. E. Perales, *Microbiol. Mol. Biol. Rev.* **2010**, 250. For selected publications on the medicinal properties of nitroarenes, see: b) M. Schmidt, M. Teitge, M. E. Castillo, T. Brandt, B. Dobner, A. Langner, *Arch. Pharm. Pharm. Chem. Life Sci.* **2008***, 341*, 624. c) R. Winkler, C. Hertweck, *ChemBioChem.* **2007**, *8*, 973. d) A. Bhattacharya, V. C. Purohit, V. Suarez, R. Tichkule, G. Parmer, F. Rinaldi, *Tetrahedron Lett.* **2006***, 47*, 1861. e) S. Rádl, P. Hezky, J. Proska, I. Krejcí, *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 13. For the application of nitroarenes in industrial biocatalysis, see: f) R. Winkler, M. Richter, U. Knüpfer, D. Merten, C. Hertweck, *Angew. Chem. Int. Ed.* **2006***, 118*, 8016.

nitropoliketide) and *Thaxtomin* (a nitro-dipeptide). Nitroaromatic compounds have also turned out to be significant in cellular signalling and in stimulating behavioural responses. For example, high 3-*nitrotyrosine* levels are usually linked to cardiovascular disease, suggesting that this molecule may be a useful indicator for certain types of physiological dysfunctions (Figure 2.1).

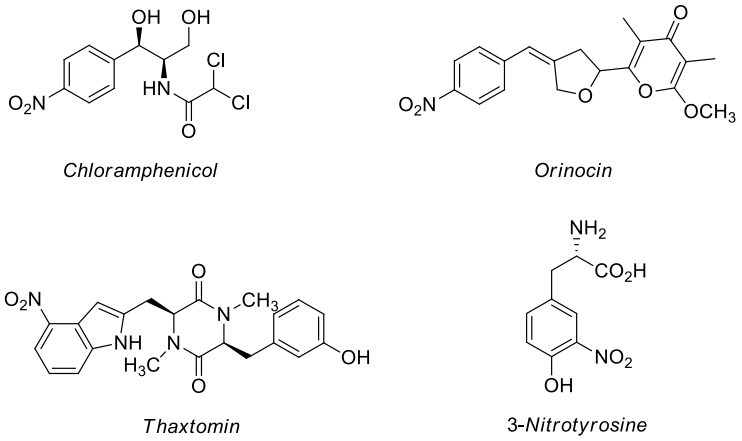


Figure 2.1

The intrinsic reactivity of the nitro group has led to the use of several nitroaromatics into high-energy explosives. The oxidation state of the nitrogen atom of the nitro group is +III and consequently, the nitrogen atom can readily accept electrons allowing nitroarenes to act as self-oxidants. As a result, energy is rapidly released from these compounds when an explosive charge is detonated. One of the first explosives was *Picric* acid. However, its corrosiveness and incomplete detonation forced chemists to develop more reactive and easy to handle structures. In contrast to *Picric* acid, *TNT* (2,4,6-trinitrotoluene) is chemically stable and insensitive to impact. Although *TNT* was widely manufactured and used in both World Wars, it is no longer produced in developed countries due to problems of

environmental contamination.[38] Other nitro-based explosives with improved thermal stability are hexanitrostilbene and *Tetryl* (Figure 2.2).[36c,39]

Nitroarenes have also been widely utilized over the years as dyes, as well as precursors of azo dyes. The early nitro dyes were acids for dyeing natural animal fibres such as wool or silk (e.g., C.I. *Acid Yellow 1*). However, the most important nitro dyes are the ones derived from nitrophenylamines, such as C.I. *Disperse Yellow 9*, because their small size is ideal for penetrating fibres such as polyester, which is a difficult fibre to dye and requires dyes with non-ionic molecular structures and relatively low water solubility, but with polar substituents for dipolar interaction with the ester moieties of the fibre. In fact, this class of dyes are named after the fact that they are dispersed rather than fully dissolved in water to carry out the dyeing process. Another example is *Disperse Blue*, which contains an azo moiety (Figure 2.2).[36c,40]

[38] Due to military applications, many areas soil and groundwater have been contaminated by *TNT*. Additionally, *TNT* and its metabolites formed during anaerobic degradation have proved to be mutagenic, for example, in *Salmonella Typhimurium* TA98 and TA100. Consequently, the development of biological processes for the treatment of nitroaromatics has been an area of active research during the last decades. For selected examples on the toxicity of some nitroaromatic compounds, see: a) R. S. Padda, C. Wang, J. B. Hughes, R. Kutty, G. N. Bennet, *Environ. Toxicol. Chem.* **2003**, *22*, 2293. b) V. Purohit, A. K. Basu, *Chem. Res. Toxicol.* **2000**, *13*, 673. For bacterial pathways of nitroaromatics degradation, see: c) Z. C. Symons, N. C. Bruce, *Nat. Prod. Rep.* **2006**, *23*, 845 and references cited therein.

[39] For selected textbooks on the explosive properties of nitroarenes, see: a) J. Akhavan, *The Chemistry of Explosives*, RSC, **2004**. b) J. A. Zukas, W. P. Walter, *Explosive effects and applications*, Springer-Verlang, New York, **1998**.

[40] For selected textbooks on the dyeing properties of nitroarenes, see: a) K. Hunger, *Industrial Dyes, Chemistry, Properties, Applications,* Wiley-VCH, Weinheim, **2003**. b) H. Zollinger, *Color Chemistry*, Wiley-VCH, New York, **1987**.

In addition to the previous described purposes, some nitro compounds are used in agriculture as fungicides, herbicides or insecticides, such as *Fluorodifen*, *Nitrofen* and *Dinoseb*, all of them derived from nitrophenol (Figure 2.2).[36c,41]

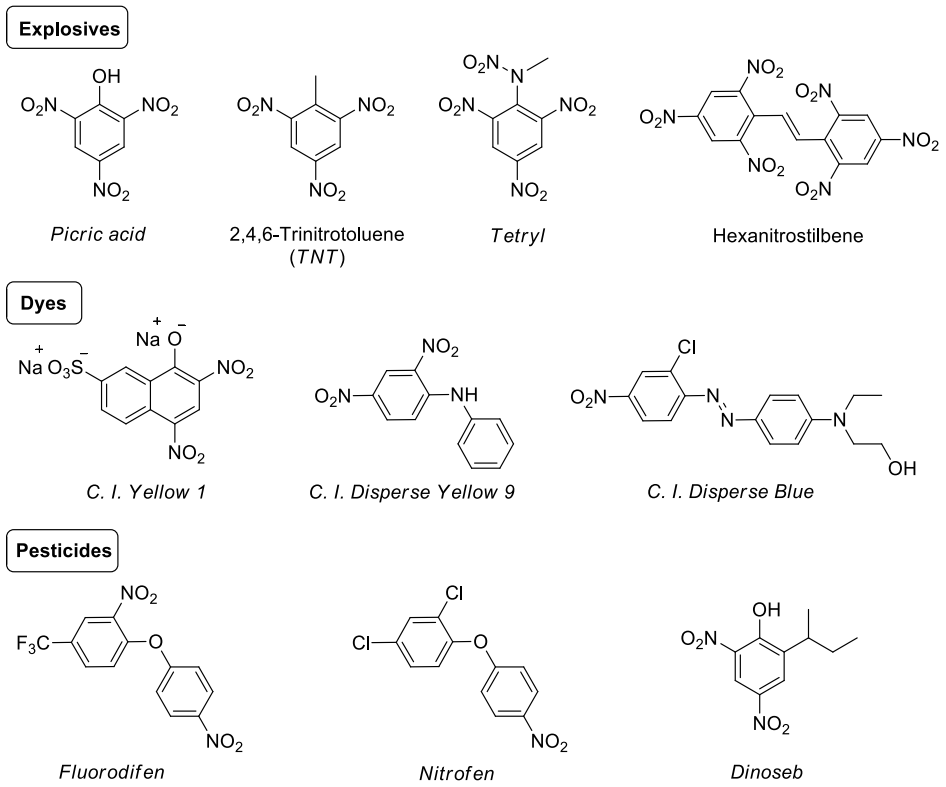


Figure 2.2

Aromatic nitro compounds are also used as versatile building blocks in synthetic organic chemistry as well as in the chemical industry. The great significance of the nitro group in organic synthesis is due to its easy availability and transformation into

[41] For selected textbooks on the application of nitroarenes as agrochemicals, see: a) C. MacBean, *The Pesticide Manual*, BCPC, **2012**. b) M. Stoytcheva, *Pesticides- Formulations, Effects, Fate*, InTech, **2011**.

other diverse functional groups. Because nitrogen-containing products can be found in a myriad of natural products and biological attractive molecules, one of the basic reactions of nitroarenes is their catalytic reduction to give aromatic amines.[42] The sequence of nitration and reduction is one of the most important tools for the preparation of arylamines, which are valuable structural motifs present in many pharmaceuticals, natural products and materials, and constitute one of the largest groups of feedstocks used by the chemical industry.[43] Additionally, as depicted in Figure 2.3, the nitro moiety of nitroarenes can be transformed into a variety of nitrogen-based functional groups such as imines,[44] azo compounds,[45] ureas,[46] isocyanates[46] and carbamates.[46,47]

[42] There are a high number of methods reported in the literature for the nitro group reduction. Among them, catalytic hydrogenation using heterogeneous transition-metal catalysis is a well-established technique and one of the most utilized strategies. For selected textbooks on heterogenous catalytic hydrogenation, see: a) H. Arnold, F. Döbert, J. Gaube, *Handbook of Heterogeneous Catalysis*, Wiley-Interscience, New York, **2008**. b) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley-Interscience, New York, **2001**. For selected recent examples on the use of H_2 as reducing agent, see: [Gold-catalyzed]; c) L. He, L. –C. Wang, H. Sun, J. Ni, Y. Cao, H. –Y. He, K. –N. Fan, *Angew. Chem. Int. Ed.* **2009**, *48*, 9538. [Platinum-catalyzed]; d) M. Li, L. Hu, X. Cao, H. Hong, J. Lu, H. Gu, *Chem. Eur. J.* **2011**, *17*, 2763. [Palladium-catalyzed]; e) J. Li, X. –Y. Shi, Y. –Y. Bi, J. –F. Wei, Z. –G. Chen, *ACS Catal.* **2011**, *1*, 657.

[43] For a selected textbook on the synthesis and application of aniline derivatives, see: Z. Rappoport, *The Chemistry of Groups, Anilines, Part 1* Patai Series: *The Chemistry of Functional*, Wiley-VCH, Chichester, UK, **2007**.

[44] a) Y. Xiang, Q. Meng, X. Li, J. Wang, *Chem. Commun.* **2010**, *46*, 5918. b) A. Zanardi, J. A. Mata, E. Peris, *Chem. Eur. J.* **2010**, *16*, 10502.

[45] H. Zhu, X. Ke, X. Yang, S. Sarina, H. Liu, *Angew. Chem. Int. Ed.* **2010**, *49*, 9657.

[46] A. M. Tafesh, J. Weiguny, *Chem. Rev.* **1996**, *96*, 2035.

[47] a) M. Gasperini, F. Ragaini, C. Cazzaniga, S. Cenini, *Adv. Synth. Catal.* **2005**, *347*, 105. b) F. Ragaini, M. Gasperini, S. Cenini, *Adv. Synth. Catal.* **2004**, *346*, 63. c) F. Ragaini, C. Cognolato, M. Gasperini, S. Cenini, *Angew. Chem. Int. Ed.* **2003**, *42*, 2886.

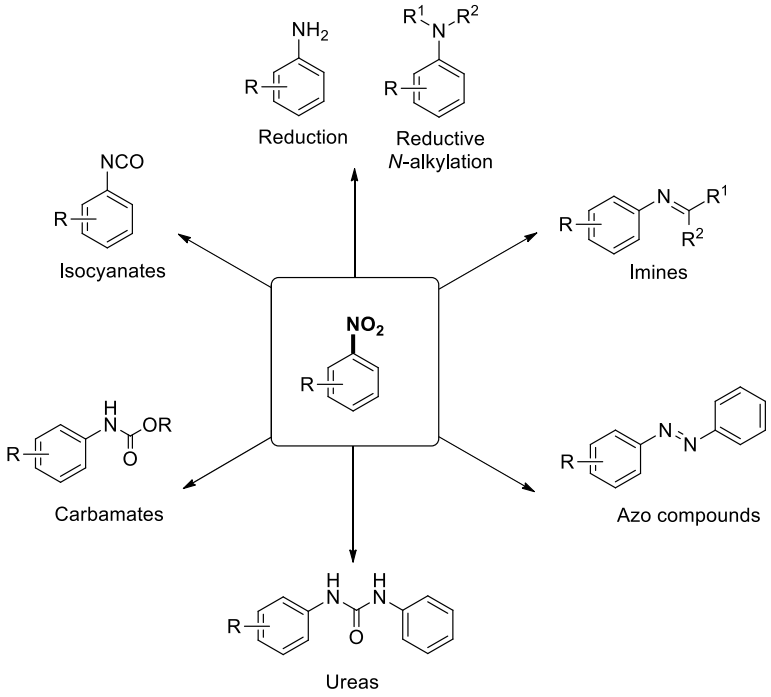
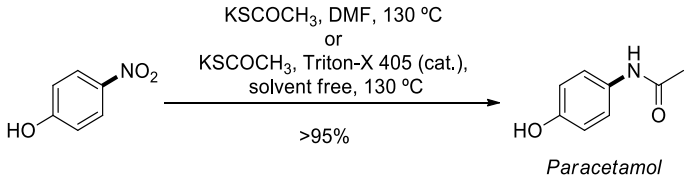


Figure 2.3

As a representative example, *Paracetamol*, also known as acetaminophen, which is sold as an analgesic and antipyretic, is produced in a one-step reductive acetamidation from *para* nitrophenol, as illustrated in Scheme 2.1.[48]



Scheme 2.1

[48] A. Bhattacharya, V. C. Purohit, V. Suarez, R. Tichkule, G. parmer, F. Rinaldi, *Tetrahedron Lett.* **2006**, *47*, 1861.

Many pharmaceuticals have their chemical origin in nitroaromatic compounds. Upon reduction of the nitro group, functionalized anilines are versatile precursors for a wide variety of heterocyclic frameworks that are privileged structures in medicinal chemistry as major source of building blocks used in drug design. By way of example, indoles, which are bioactive compounds not only of drugs but also of agrochemicals,[49] or phenotiazines, a large class of drugs with antipsychotic properties, are easily assembled from *ortho*-functionalized nitroarenes.[50] Other relevant heterocycle architectures readily available from nitroarenes are benzimidazoles, benzoxazoles and benzothiazoles, which are also structural motifs that form the core of many products with pharmacological relevance (Figure 2.4).[51]

[49] For a review on the biological importance of indoles, see: a) N. K. Kaushik, N. Kausnik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013***, 18*, 6620. For selected publications on the synthesis of indoles under reductive conditions from nitroaromatic compounds, see: b) L. Wylie, P. Innocenti, D. K. Whelligan, S. Hoelder, *Org. Biomol. Chem.* **2012**, *10*, 4441. c) Y. Yamane, X. Liu, A. Hamasaki, T. Ishida, M. Haruta, T. Yokoyama, M. Tokunaga, *Org. Lett.* **2009**, *11*, 5162. d) F. Ragaini, A. Rapetti, E. Visentin, M. Monzani, A. Caselli, S. Cenini, *J. Org. Chem.* **2006**, *71*, 3748. e) A. Penoni, J. Volkmann, K. M. Nicholas, *Org. Lett.* **2002**, *4*, 699. f) A. Penoni, K. M. Nicholas, *Chem. Commun.* **2002**, 484.

[50] For selected publications on the application of phenotiazine derivatives, see: a) C. Korth, B. C. H. May, F. E. Cohen, S. B. Prusiner, *Proc. Natl. Acad. Sci. U. S. A.*, **2001**, *98*, 9836. b) J. Y. Melvin, R. M. Jefferson, *J. Med. Chem.* **1992**, *35*, 716. For selected publications on the synthesis of phenothiazine derivates under reductive conditions from nitroaromatic compounds, see: c) R. O. Hutchins, D. W. Lamson, L. Rua, C. Milewski, B. Maryanoff, *J. Org. Chem*, **1971**, *36*, 803. d) J. I. G. Cadogan, R. K. Mackie, M. J. Todd, *Chem. Commun. (London)*, **1966**, 491a. e) S. P. Massie, *Chem. Rev.* **1954**, *54*, 797.

[51] For selected publications on the application of benzimidazoles, benzoxazoles and benzothiazoles, see: a) A. Puratchikody, G. Nagalakshmi, M. Doble, *Chem. Phar. Bull.* **2008***,* *56*, 273. b) T. Ishida, T. Suzuki, S. Hirashima, K. Mizutani, A. Yoshida, I. Ando, S. Ikeda, T. Adachi, H. Hashimoto, *Bioorg. Med. Chem. Lett.* **2006***, 16*, 1859. c) R. Morphy, Z. Rankovic, *J. Med. Chem.* **2005***, 48*, 6523. d) N. H. Hauel, H. Nar, H. Priepke, U. Ries, J. –M. Stassen, W. Wienen, *J. Med. Chem.* **2002***, 45*, 1757. e) R. R. Wexler, W. J. Greenlee, J. D. Irvin, M. R. Goldberg, K. Prendergast, R. D. Smith, P. B. M. W. M. Timmermans, *J. Med. Chem.* **1996**, *39*, 625. For selected publications on the synthesis of benzimidazoles under reductive conditions from nitroaromatic compounds, see: f) T. B. Nguyen, L. Ermolenko, A. Al-Mourabit, *J. Am. Chem. Soc.* **2013**, *135,* 118. g) J. Kim, J. Kim, H. Lee, B. M. Lee,

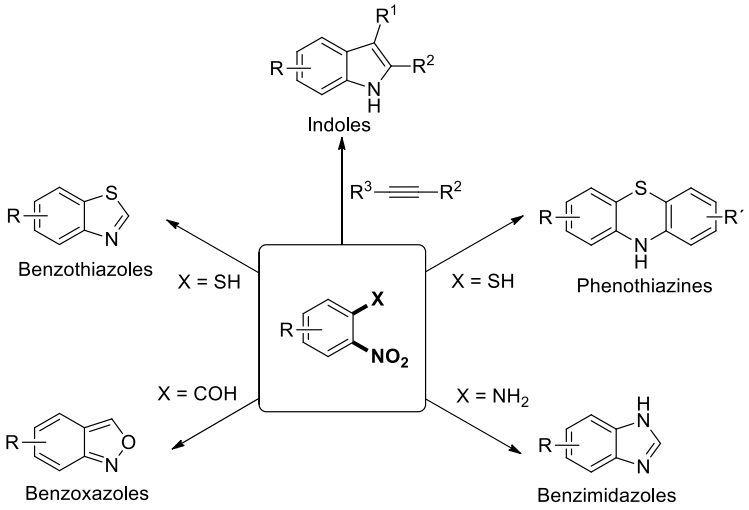


Figure 2.4

2.2. The nitration reaction

The exceptional significance and versatility in organic synthesis, medical chemistry, material science and chemical industry continues to inspire considerable interest in the development of new methods for the synthesis of nitroaromatic compounds.[52]

B. H. Kim, *Tetrahedron*, **2011**, *67*, 8027. h) E. Cuevas, M. Kosaka, T. Muramatsu, M. Kobayashi, T. IIzuka, T. Horaguchi, *J. Heterocyclic Chem.* **2009**, *46*, 1309. i) K. R. Hornberger, G. M: Adjabeng, H. D. Dickson, R. G. Davis-Ward, *Tetrahedron Lett.* **2006**, *47*, 5359. j) D. S. VanVliet, P. Gillespie, J. J. Scicinski, *Tetrahedron Lett.* **2005**, *46*, 6741. For selected publications on the synthesis of benzoxazoles under reductive conditions from nitroaromatic compounds, see: k) J. Chauhan, S. Fletcher, *Tetrahedron Lett.* **2012**, *53*, 4951. l) R. Han, K. I. Son, G. H. Ahn, Y. M. Jun, B. M. Lee, Y. Park, B. H. Kim, *Tetrahedron Lett.* **2006**, *47*, 7295. m) B. H. Kim, Y. Jin, Y. M. Jun, R. Han, W. Baik, B. M. Lee, *Tetrahedron Lett.* **2000**, *41*, 2137.

[52] For a review on recent advances in the nitration of arenes, see: a) G. Yan, M. Yang, *Org. Biomol. Chem.* **2013**, *11*, 2554. For selected textbooks, see: b) J. G. Hoggett, R. B. Moodie, J. R. Penton, K. Schofield, *Nitration and Aromatic Reactivity,* Cambridge University Press, Cambridge, **2009**. c) G. A.

2.2.1. The early history

In 1834, Mitscherlich reported the first aromatic nitro compounds by treating hydrocarbons derived from coal with fuming nitric acid.[53] However, it is believed that Faraday was the first to perform the nitration of benzene since he reported in his notes that a substance with scent of bitter almond (nitrobenzene) was formed when adding nitric acid to benzene.[54] After some subsequent isolated examples of nitration reaction, as early as in 1845, a systematic study on the nitration of benzene to give mono- and dinitrobenzenes by using a mixture of nitric acid and sulphuric acid ("mixed acid") was reported by Hofmann and Muspratt.[55] In 1847, the production of nitrobenzene from coal was patented and the manufacture of nitrobenzene using the "mixed acid" process began in France in 1848 by Mansfield.[56] The serendipitous discovery of the first synthetic organic chemical dye *Mauveine* (also known as purple aniline and Perkin´s mauve) in 1856 started the European aniline dye industry that became the basis for a worldwide synthetic dye industry.[57]

Olah, R. Malhorta, S. C. Narang, *Nitration: Methods and Mechanism*, Wiley-Blackwell, Hoboken, **1989**. d) A. V. Topchiev, *Nitration of Hydrocarbons and Other Organic Compounds*, Pergamon Press, **1959**. e) E. J. Hoffman, *The nitration of toluene*, University of Michigan Reprints, **1916**.

[53] a) E. Mitscherlich, *Annln. Phys. Chem.* **1834**, *31*, 625. b) E. Mitscherlich, *Annln. Pharm*, **1834**, 305.

[54] M. Faraday, *Phil. Trans. R. Soc. Lond.* **1825**, *115,* 440.

[55] For the first patent regarding the nitration using the "mixed acid", see: a) Hofmann, Muspratt, *Liebigs Ann. Chem.* **1846**, *57*, 201. For another selected patent regarding the nitration of aromatic compounds catalyzed by sulphuric acid, see: b) H. E. Roscoe, C. Schorlemmer, *A Treatise on Chemistry* vol3, **1981**.

[56] a) C. B. Mansfield, *Annalen der Chemie und Pharmacie*, **1849**, *69*, 162. For a selected textbook on the industrial synthesis of nitrobenzene, see: b) H. –G. Franck, J. W. Stadelhofer, *Industrial Aromatic Chemistry*, Springer-Verlag, Berlin, Heidelberg, **1988**.

[57] K. Hubner, *Chemie in unserer Zeit*, **2006**, *40*, 274.

2.2.2. Classical electrophilic nitration of arenes

- ***The "mixed acid" system (H_2SO_4/HNO_3)***

➢ ***Reactivity and regioselectivity***

Aromatic nitration is probably the electrophilic aromatic reaction that has been more deeply studied. The introduction of the nitro group into aromatic compounds is usually effected using either concentrated nitric acid or a mixture of concentrated sulphuric acid and nitric acid (generally called the "mixed acid" method), depending on the reactivity of the substrate. For electron-rich aromatic substrates (e.g., phenols) even dilute nitric acid may be sufficient, but for electron-neutral or electron-poor aromatic derivatives, forcing conditions with "mixed acid" are usually needed.[36,52] Nitration reactions are frequently carried out in neat conditions using the acid mixture as solvent.

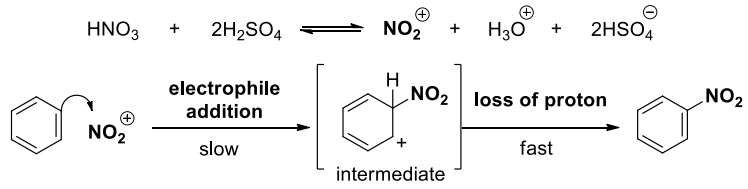
The sulphuric acid is believed to catalyze the formation of the nitronium ion (NO_2^+), which is the electrophile species that is involved in the electrophilic substitution (Scheme 2.2). Other strong acids, such as H_2PO_4, polyphosphoric acid, $HClO_4$, HF, BF_3, CH_3SO_3H, CF_3SO_3H or FSO_3H, have also proved to be very effective.[58] The poor performance of HNO_3 on its own in nitrating benzene can thus be attributed to the much lower amount of available NO_2^+ ions.[59] Additionally, the presence of the acid catalyst not only enhances the nitrating action of nitric acid but also diminishes its oxidizing properties and removes water from the reaction media.

[58] a) E. Dal, N. L. Lancaster, *Org. Biomol. Chem.* **2005**, *3*, 682. b) G. A. Olah, A. Orlinkov, A. B. Oyzoglov, G. K. S. Prakash, *J. Org. Chem*. **1995**, *60*, 7348. c) G. A. Olah, V. Reddy, G. K. S. Prakash, *Synthesis* **1992**, 1087. d) P. S. Varma, D. A. Kulkarmi, *J. Am. Chem. Soc.* **1925***, 47*, 143.

[59] The small amount of NO_2^+ can be reasoned through a two stage process illustrated as follows:

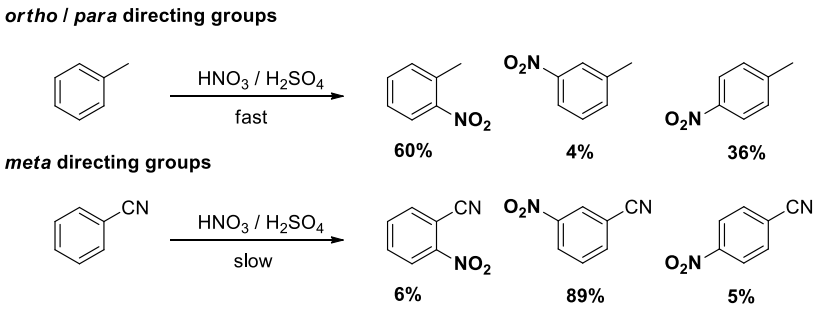
$$HO\text{-}NO_2 + HNO_3 \overset{\text{fast}}{\rightleftharpoons} H_2\overset{\oplus}{O}\text{-}NO_2 + \overset{\ominus}{NO_3}$$

$$H_2\overset{\oplus}{O}\text{-}NO_2 + HNO_3 \overset{\text{slow}}{\rightleftharpoons} H_3\overset{\oplus}{O} + \overset{\ominus}{NO_3} + \mathbf{\overset{\oplus}{NO_2}}$$



Scheme 2.2

The relative rate and the regioselectivity of the reaction are determined by the nature of the substituents in the aromatic ring, which can generally be divided in two groups: a) activating groups and b) deactivating groups. Activating groups stabilize the cationic intermediate formed during the substitution by donating electrons into the aromatic system by either inductive and/or resonance effect. This extra electron density delivered to the aromatic system not only increases the reaction rate, but also is concentrated at the *ortho* and *para* positions, making them more reactive towards the electrophile. For example, due to the presence of the activating methyl group, toluene is nitrated 25 times faster than benzene, whereas in the case of phenol, the nitration occurs 1000 times faster. On the other hand, deactivating groups destabilize the intermediate cation and consequently the reaction rate is decreased. In this case, the *meta*- position is the most favourable to conduct the electrophilic substitution. Scheme 2.3 exemplifies the nitration of toluene and cyanobenzene under these conditions.

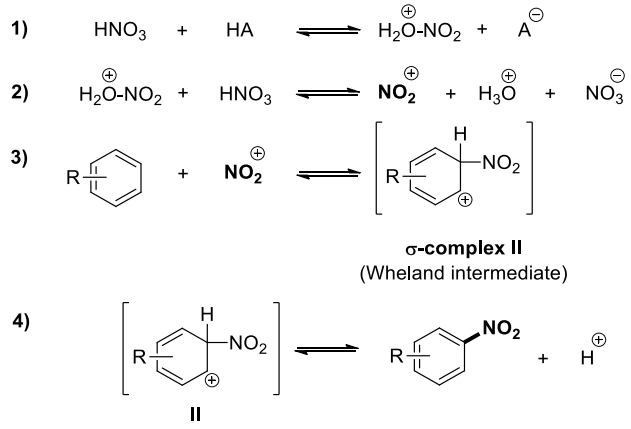


Scheme 2.3

However, some substituents, such as the halogens, withdraw electrons inductively, but they are donors by resonance. On the balance, the inductive effect gains, rendering the halobenzenes deactivated (chlorobenzene reacts 30 times slower than benzene). Nevertheless, because of their resonance effect, these substituents direct the incoming NO_2^+ electrophile to the *ortho*- and *para*- positions.

- ***Mechanistic considerations***

Although aromatic nitration is considered as a mechanistically well-defined organic reaction, decisive mechanistic aspects are still evolving. The fundamental mechanism of electrophilic nitration was elucidated by Ingold and Hughes in 1950.[60] The accepted mechanism, as illustrated bellow in Scheme 2.4, consists of four steps.



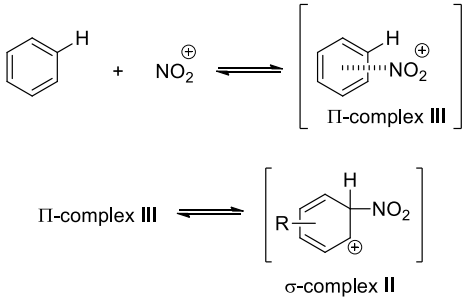
Scheme 2.4

The first two steps involve the acid (HA)-catalyzed transformation of nitric acid into the nitronium ion (NO_2^+). Aromatic molecules of modest reactivity exhibit second order kinetics in mixtures of nitric acid with a strong acid (sulfuric acid).[59] Under these

[60] a) C. K. Ingold, E. D. Hughes, *J. Chem. Soc.* **1950**, 2400. See also: b) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, New York, **1969**. For a recent study of electrophilic aromatic substitution see: c) W. F. K. Schnatter, D. W. Rogers, A. A. Zavitsas, *J. Phys. Chem. A*, **2013**, *117*, 13079.

conditions, NO_2^+ ion is formed in a rapid pre-equilibrium, prior to the electrophilic attack to the aromatic ring, which is the rate determining step, forming a σ-complex **II**. Finally, the highly reactive arenium ion rapidly deprotonates in the last irreversible step, regenerating both the aromaticity and the acid catalyst, yielding the expected nitroaromatic compound $ArNO_2$. This fast deprotonation can be confirmed by the absence of a primary isotope effect when deuterium is introduced at the substitution site.

For the third step of the mechanistic proposal, involving the formation of the Wheland intermediate **II**, Olah suggested that, in the case of reactive alkyl-substituted aromatic compounds, the original Ingold-Hughes mechanism had to be modified by invoking two separate intermediates with an additional π-complex **III** formation.[61]



Scheme 2.5

Schofield also proposed the formation of a π-complex intermediate **III**.[62] Their proposal is similar to that of Olah, except for the nature of the presumed π-complex **III**. In Schofield´s mechanism, the intermediate is considered to be an encounter pair which does not involve any bonding interaction between the reactive species but, rather, is held together only by the solvent cage.

[61] a) G. A. Olah, *Acc. Chem. Res.* **1971**, *4*, 240. b) G. A: Olah, S. Khun, S. H. J. Flood, *J. Am. Soc. Chem.* **1961**, *83*, 4571.

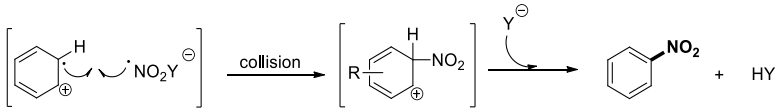
[62] a) R. D. Coombes, R. D. Moodie, K. Schofield, *J. Chem. Soc. B*. **1968**, 800. See also: b) K. Schofield, *Aromatic Nitration*, Cabridge University Press, Cambridge, **1980**.

More recently, a theoretical study by Olah and co-workers suggests three separate intermediates on the potential diagram of the reaction for the third step (electrophilic substitution) of the Ingold-Hughes mechanism.[63] In this study the interaction between benzene and the NO_2^+ ion was investigated and it was observed that first a T-shaped π-complex **(III)** is formed due to an electrostatic interaction between NO_2^+ ion and the aromatic π-cloud, where one of the oxygen atoms of the NO_2^+ ion interacts with the arene with a bond angle of 180.0º. The second intermediate **(IV)** is generated after single-electron transfer from the arene ring to the NO_2^+ ion and shows the characteristics of an intimate pair of the aromatic cation-radical and the $NO_2^{\bullet}$ radical.[64] In this case, the O–N–O bond angle is 136.7º, quite close to the angle of an isolated NO_2 molecule (134.1º), which indicates that the NO_2 moiety is strongly interacting with the benzene π-system indicating that single-electron transfer from benzene to the NO_2^+ has already occurred in this geometry.[65] This intermediate, then, collapses and leads to the conventional σ-complex **II**

[63] P. M. Esteves, J. W. de M. Carneiro, S. P. Cardoso, A. G. H. Barbosa, K. K. Laali, G. Rasul, G. K. S. Prakash, G. A. Olah, *J. Am. Chem. Soc.* **2003**, *125*, 4836.

[64] For other selected examples based on the one-electron-transfer pathway, see: a) C. L. Perrin, *J. Am. Chem. Soc.* **1977**, *99*, 5516. b) J. Weiss, *J. Trans. Faraday Soc.* **1946**, *42*, 116. c) J. Kenner, *Nature*, **1945**, *156*, 369.

[65] This proposal was also corroborated by Kochi when studying the reaction of electron-rich arenes with nitronium ion carrying species (NO_2Y). A donating-accepting interaction between the arene and the NO_2Y results in the formation of a charge transfer complex [ArH, NO_2Y]. The rate-determining step is the formation of the ion pair [$ArH^{+\bullet}$, $NO_2Y^{-\bullet}$] by photoactivation. The aromatic containing radical collapses with the $NO_2^{\bullet}$ radical into the σ-complex **II**, see: a) E. K. Tim, T. M. Bockman, J. K. Kochi, *J. Am. Chem. Soc.* **1993**, *115*, 3091.



σ-complex **II**

(Wheland intermediate).[66] The different intermediates (**III**, **IV** and **II**, respectively) are illustrated bellow in Figure 2.5.

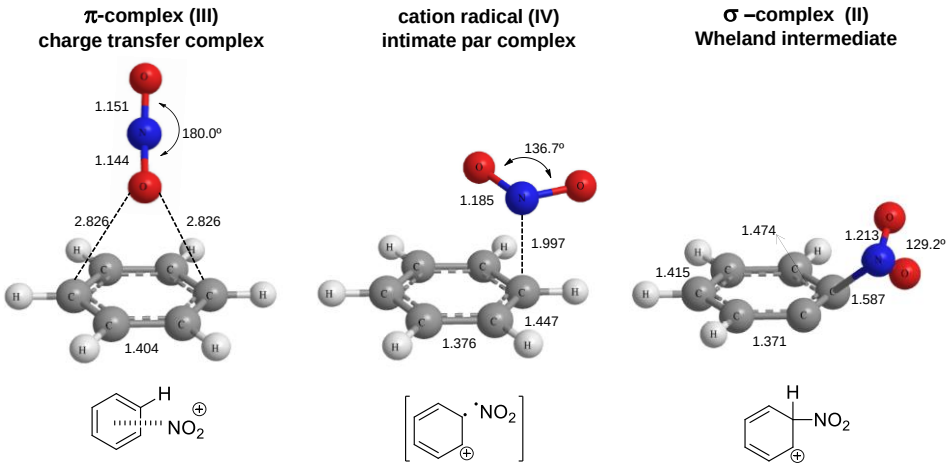
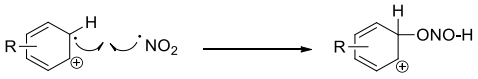


Figure 2.5

- ***Nitration with Nitrogen Oxides***

Nitrogen oxides such as N_2O_5, N_2O_3, N_2O_4/NO_2 and NO has been reported as nitrating agents for aromatic compounds.[36c,52,67] Amongst these nitrogen oxides, the

[66] In a recent study regarding the polar mechanism for the nitration of benzene, Parker suggested an alternative pathway. Collapse of the $ArH^{\bullet+}/^{\bullet}NO_2$ pair results in a σ complex **II´** with C–O rather than C–N bonding, see: V. D. Parker, T. Kar, D. Bethell, *J. Org. Chem.* **2013**, *78*, 9522.

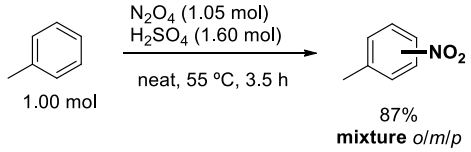


σ-complex **II´**

[67] For a recent review regarding the application of N_2O_4/NO_2, see: a) M. Shiri, M. A. Zolfigol, H. G. Kruger, Z. Tanbakouchian, *Tetrahedron Lett.* **2010**, *66*, 9077 and references cited therein. See also: b) P. Gray, A. D. Yoffe, *Chem. Rev.* **1955**, *55*, 1069. c) J. L. Riebsomer, *Chem. Rev.* **1945**, *36*, 157. d) L. B. Haines, K. Adkins, *J. Org. Chem. Soc.* **1925**, *47*, 1419.

N_2O_4/NO_2 system has widely been used due to its powerfulness and cost effectiveness.

In 1930 Pinck reported the nitration of aromatic compounds with N_2O_4 and H_2SO_4 by adding one mol of toluene to a solution of 1.05 mol of N_2O_4 in 1.60 mol of H_2SO_4.[68] Upon stirring the reaction mixture for 3.5 h at 55 ºC, the excess of toluene was removed by distillation to afford nitrotoluene in 87% yield (no observation about the regioselectivity was made).



Scheme 2.6

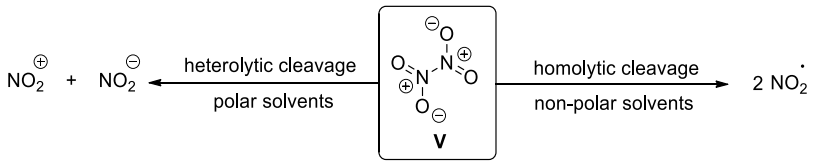
Titov and Baryshnikova also studied the system N_2O_4/H_2SO_4 as nitrating agent and showed that the reaction proceeded by the ionization of N_2O_4 into nitrosonium and nitronium ion, where only the latter one was considered to be the effective nitrating agent.[69] However, N_2O_4 alone can only be used as nitrating agent for the nitration of activated aromatics like phenol, polymethylated benzenes and polycyclic aromatics.[67,70]These reactions have been proposed to occur *via* nitrosation (NO^+).[71]

[68] a) L. A. Pinck, *Ind. Eng. Chem.* **1930**, *22*, 1241. b) L. A. Pinck, *J. Am. Chem. Soc.* **1927**, *49*, 2536.

[69] Baryshnikova, Titov, *Doklay Akad. Nauk SSSR,* **1953**, *91*, 1099.

[70] Nitration can also be carried out without acid catalysis under homolytic radical nitration conditions. For example, The *Kyodai* nitration, which was reported by Suzuki in 1991 as a mixture of nitrogen dioxide and ozone, is considered to be as one of the most powerful nitrating systems under non-acidic conditions even for those non-activated aromatic systems. The proposed mechanism consists of the reaction of NO_2 with O_3 to form a NO_3 radical, which oxidises the aromatic compound to form a radical cation. This radical cation reacts with NO_2 yielding the desired nitroarene. However, this method suffers from low regioselectivity: H. Suzuki, T. Murashima, K. Shimizu, K. Tsukamoto, *Chem. Lett.* **1991**, 817.

Under almost all conditions, molecular nitrogen dioxide can be considered as an equilibrium with the predominant dimer form, the planar and symmetrical structure **V**, which under non-polar conditions homolytically dissociates into two $NO_2^{\bullet}$ radical species while a heterolytic dissociation to NO_2^+ and NO_2^- takes place under polar conditions.[52d,72]



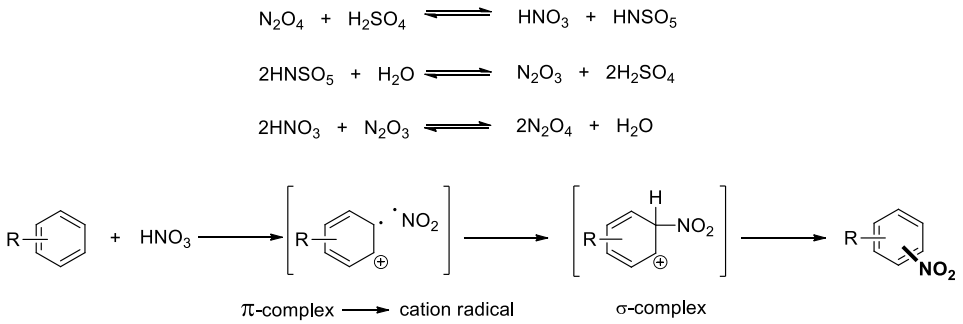
Scheme 2.7

In the case of the N_2O_4/H_2SO_4 system, the nitration occurs at the expense of nitric acid formation during the interaction of nitrogen dioxide with sulphuric acid as exemplified in Scheme 2.8.

The proposed Kyodai nitration mechanism is depicted bellow:

[71] The oxidation of nitrosoarenes by an external oxidant or by autoxidation can also be a protocol for the synthesis of nitro aromatic compounds. For a comprehensive review on the preparation of C-Nitroso compounds, see: a) B. G. Gowenlock, G. B. Richter-Addo, *Chem. Rev.* **2004**, *104*, 3315. See also: b) J. Hartung, *Chem. Rev.* **2009**, *109*, 4500. c) H. D. Larson, *The Chemistry of the Nitro and Nitroso Group*, part 1, (Ed: H. Fever), Wiley, New York, **1969**. For an analysis of the intermediates in the autoxidation of nitrogen monoxide, see: d) B. Galliker, R. Kissner, T. Nauser, W. H. Koppenol, *Chem. Eur. J.* **2009**, *15*, 6161.

[72] J. H. Ridd, *Acta Chemica Scandinavica*, **1998**, *52*, 11.



Scheme 2.8

The main disadvantage of using nitrogen oxides is their toxicity. Breathing low levels of nitrogen oxides may cause cough, shortness of breath, tiredness and nausea.[73] Additionally, the lack of regiocontrol as well as the use of acidic solvents for the less reactive substrates encouraged the research community to find less toxic and easy to handle nitrating sources.

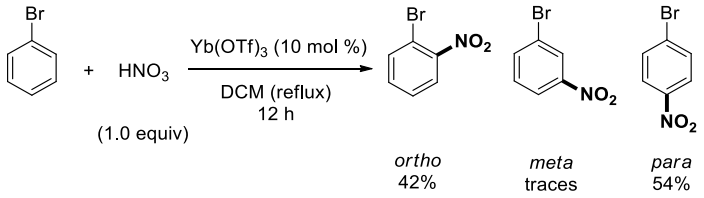
- ***Milder nitration protocols: combination of HNO_3 or nitrogen oxides with strong Lewis acids or acidic solid supports***

The amount of nitric acid could be reduced to 1.0-3.0 equivalents when catalytic amounts of lanthanide triflates/nosylates or mixed catalysts of rare earth metals salts with other additives were added.[74] Although the amount of nitric acid is significantly

[73] N. M. Elsayed, *Toxicology*, **1994**, *89*, 161.

[74] For selected examples on the combination of HNO_3 with strong Lewis acids, see: a) M. M. Heravi, K. Bakhtiari, T. Benmorad, F. F. Bamoharram, H. A. Oskooie, M. H. Tehrani, *Monatsch. Chem.* **2007**, *138*, 449. b) T. N. Parac-Vogt, B. Binnemans, *Tetrahedron Lett.* **2004**, *45*, 3137. c) M. Shi, S. –C. Cui, *Adv. Synth. Catal.* **2003**, *345*, 1329. d) M. Shi, S. –C. Cui, *Chem. Commun.* **2002**, 994. e) M. Shi, S. –C. Cui, *J. Fluorine Chem.* **2002**, *113*, 207. f) C. G. Frost, J. P. Hartley, D. Griffin, *Tetrahedron Lett.* **2002**, *43*, 4789. g) F. J. Waller, A. G. M. Barrett, D. C. Braddock, D. Ramprasad, *Chem. Commun.* **1997**, 613. For selected examples on the combination of nitrogen oxides with strong Lewis acids, see: [BF_3]; h) G. B. Bachman, C. M. Vogt, *J. Am. Chem. Soc.* **1958**, *80*, 2987. i) G. B. Bachman, H. Fever, B. R. Bluestein, C. M. Vogt, *J. Am. Chem. Soc.* **1955**, *77*, 6188. [$Ln(OTf)_3$]; j) X. Du, X. Li, Z. Xu,

diminished, the use of expensive and toxic catalysts and the lack of both regiochemical control and functional group tolerance, make this alternative highly limited. For example, bromobenzene was nitrated using 1.0 equivalent of HNO_3 and a catalytic amount of $Yb(OTf)_3$ (10 mol%) in a DCM refluxing mixture for 12 h, yielding a mixture of *ortho* and *para*-nitro derivatives in approximately equal ratios. Additionally, in general, these conditions are not compatible with arenes containing basic heteroatoms, such as anilines, because the Lewis acid species does not remain active due to its interaction with the basic nitrogen.



Scheme 2.9

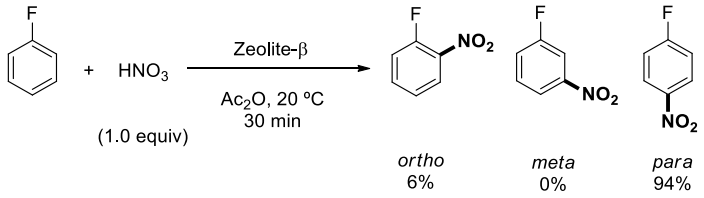
The use of solid acid supports has also been studied in an attempt of reducing the large amount of acids. They are potentially attractive because of the ease of removal and recycling of the catalyst and the possibility that the solid might influence the selectivity. In 1978 Olah reported the use of Nafion-H and other polysulfonic acid resins which catalyzed the nitration of arenes with poor regioselectivity.[75] Different zeolites, which previously must be activated with an acidic source, have been screened for solid catalysis aromatic nitration.[76] For example, alkylbenzenes and

Synth. Commun. **2007**, *37*, 3741. [Iron(III) complexes]; k) R. R. Bak, A. J. Smallridge, *Tetrahedron Lett.* **2001**, *42*, 6767. l) H. Suzuki, S. Yonezawa, N. Nonoyema, T. Mori, *J. Chem. Soc. Perkin Trans. 1*, **1996**, 2385.

[75] G. A. Olah, R. Malhotra, S. C. Narang, *J. Org. Chem.* **1978**, *43*, 4628.

[76] For a selected textbook on the nitration of aromatic compounds using zeolites as catalysts, see: a) E. G. Derouane, *Catalyst for Fine Chemical Synthesis*, *Microporus and Mesoporus Solid Catalysts*, Volume 4, Chapter 5, A. Corma, S. Iborra, *Nitration of Aromatic Compounds*, WILEY & Sons, Chichester, **2006**. For selected examples on the nitration of aromatic compounds with stoichiometric amounts of HNO_3 catalyzed by zeolites, see: b) R. J. Kalbasi, M. Ghiaci, A. R. Massah, *Appl. Catal.*

halogenobenzenes are regioselectively nitrated at the *para* position using zeolite β as a catalyst and stoichiometric amounts of nitric acid.[76e,f] (Scheme 2.4).



Scheme 2.10

2.2.3. Alternative nitration protocols

Recently, much attention has been devoted to the development of greener nitrating agents in order to improve the nitration of aromatic compounds and avoid their waste treatment. The utilization of nitrate salts and ipso-nitration strategies have emerged as powerful alternatives to the classical methods.

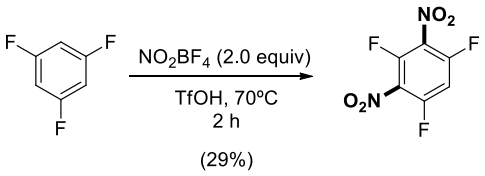
- ***Nitrate/nitronium salts as "NO_2" source***

In 1925 Hantsch synthesized a perchlorate nitronium salt from the reaction of nitric and perchloric acids. However this compound was unstable and highly explosive. Olah and Kuhn circumvented this problem by changing the counter ion to tetrafluoroborate (NO_2BF_4) and hexafluoroantimoniate (NO_2SbF_6).[77] This type of

A. **2009***, 353*, 1. c) K. Smith, T. Gibbins, R. W. Millar, R. P. Claridge, *J. Chem. Soc. Perkin Trans. 1.*, **2000**, 2753. d) B. M. Choudary, M. Sateesh, M. L. Kantam, K. K. Rao, K. V. R. Prasad, K. V. Raghavan, J. A. R. P. Sarma, *Chem. Commun.* **2000**, 25. e) K. Smith, A. Musson, G. A. DeBoos, *J. Org. Chem.* **1998**, *63*, 8448. f) K. Smith, A. Musson, G. A. DeBoos, *Chem. Commun.* **1996**, 469. For selected examples on the nitration of aromatic compounds with nitrogen oxides catalyzed by zeolites, see: g) X. Peng, H. Suzuki, *Org. Lett.* **2001**, *3*, 3431. h) K. Smith, S. Almeer, C. Peters, *Chem. Commun.* **2001**, 2748. i) X. Peng, H. Suzuki, C. Lu, *Tetrahedron Lett.* **2001**, *42*, 4357. j) K. Smith, S. Almeer, S. J. Black, *Chem. Commun.* **2000**, 1571.

[77] a) G. A. Olah, S. C. Narang, J. A. Olah, K. Lammertsma, *Proc. Natl. Acad. Sci. USA*, **1982***, 79*, 4487. b) G. A. Olah, S. J. Kuhn, *J. Am. Chem. Soc.* **1962**, *84*, 3684. See also: c) G. A. Olah, D. A.

nitronium salts were found to be extremely active nitrating agents for aromatics, although their activity is heavily dependent on the solvent and temperature.[52b] Whereas activated aromatic systems are efficiently nitrated by nitronium salts in aprotic media and low temperatures, when electron-withdrawing groups are present in the arene, the electrophilic nitration of these compounds with nitronium salts is much more difficult and in many cases requires super acidic media (TfOH) as solvent, as evidenced in the example depicted in Scheme 2.11.[78,79]



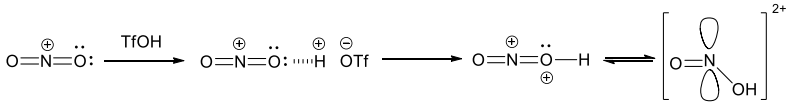
Scheme 2.11

Among the first nitration examples, where the excess of acid mixtures or nitrogen oxides was avoided by using stoichiometric amounts of inorganic salts, stand out those reported by Flewett and Wood using, respectively, $Ti(NO_3)_4$,[80] and $VO(NO_3)_3$[81] as stoichiometric nitrating agents. Although excellent yields were achieved, a total

Klumpp, *Superelectrophiles and their Chemistry*, John Wiley & Sons, Inc,. Hoboken, New Yersey, **2008**.

[78] G. A. Olah, K. K. Laali, G. Sandford, *Proc. Natl. Acad. Sci. USA*, **1992**, *89*, 6670.

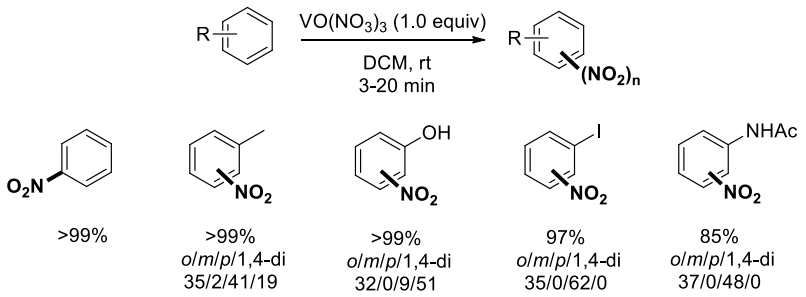
[79] The increased reactivity of the nitronium ion in super acidic media can be rationalized in terms of its protosolvation. The protonated oxygen lone pair diminishes the N–O π-bond character, leading to partial electron deficiency at the nitrogen *p* orbital and bending of the nitronium ion, which lowers the activation barrier for bonding interaction with the π aromatic ring.



[80] D. W. Amos, D. A. Baines, G. W. Flewett, *Tetrahedron Lett.* **1973**, 3191.

[81] M. F. A. Dove, B. Manz, J. Montgomery, G. Pattenden, S. A. Wood, *J. Chem. Soc. Perkin Trans. 1*, **1998**, 1589.

loss in the regioselectivity was observed, yielding mixtures of mono-(*ortho*- and *para*-) and di-nitrated compounds, (Scheme 2.12).



Scheme 2.12

Since then, many other inorganic salts have emerged as "greener" nitro sources, such as, $Bi(NO_3)_3{\cdot}5H_2O$,[82] $Ca(NO_3)_2$,[83] $Ni(NO_3)_2{\cdot}6H_2O$/*p*-TSA,[84] $Fe(NO_3)_3$,[85] $NaNO_3$,[86] KNO_3[87], $(NH_4)_2Ce(NO_3)_6$ (CAN)[88] and $AgNO_3$.[89] However, the vast majority of the

[82] a) A. Bose, W. P. Sanjoto, S. Villarreal, H. Aguilar, B. K. Banik, *Tetrahedron Lett.* **2007**, *48,* 3945. b) H. –B. Sun, R. Hua, Y. Yin, *J. Org. Chem.* **2005**, *70*, 9071. c) S. Samajdar, F. F. Becker, B. K. Banik, *Tetrahedron Lett.* **2000**, *41*, 8017.

[83] A. K. Bose, S. N. Ganguly, M. S. Manhas, S. Rao, J. Speck, U. Pekelny, E. Pombo-Villars, *Tetrahedron Lett.* **2006**, *47*, 1885.

[84] V. Anuradha, P. V. Srinivas, P. Aparna, J. M. Rao, *Tetrahedron Lett.* **2006**, *47*, 4933.

[85] R. Rajagopal, K. V. Srinivasan, *Synth. Commun.* **2003**, *33*, 961.

[86] a) [$NaNO_3$/$Mg(HSO_4)$]; M. A. Zolfigol, E. Ghaemi, E. Madrakian, *Molecules*, **2001**, *6*, 614. b) [$NaNO_2$/trichloroisocyanuric acid]; M. A. Zolfigol, E. Madrakian, E. Ghaemi, *Synlett.* **2003**, 191. c) [$NaNO_2$/H_2SO_4.SiO_2]; M. A. Zolfigol, E. Madrakian, E. Ghaemi, *Molecules* **2002**, *7*, 734. For the nitration of a Ru^{III}(salen) complex with $NaNO_2$/NaOH, see: d) B. Birkmann, B. T. Owens, S. Bandyopadhyay, G. Wu, P. C. Ford, *J. Inorganic Biochem.* **2009**, *103*, 237.

[87] P. Strazzolini, A. G. Guamanini, A. Runcio, *Tetrahedron Lett.* **2001**, *42*, 1387.

[88] a) X. Yang, C. Xi, Y. Jiang, *Tetrahedron Lett.* **2005***, 46*, 8781. b) J. M. Mellor, S. Mittoo, R. Parkes, R. W. Millar, *Tetrahedron Lett.* **2000**, *56*, 8019. c) S. Dintürk, J. H. Ridd, *J. Chem. Soc. Perkin Trans. 2*, **1982**, 961.

[89] a) [$AgNO_3$/NBS]; N. Nowrouzi, A. M. Mehrnpour, E. Bashiri, Z. Shayan, *Tetrahedron Lett.* **2012**, *53*, 4841. b) [$AgNO_3$/PPh_3/Br_2]; N. Iranpoor, H. Firouzabadi, N. Nowrouzi, D. Firouzabadi, *Tetrahedron*

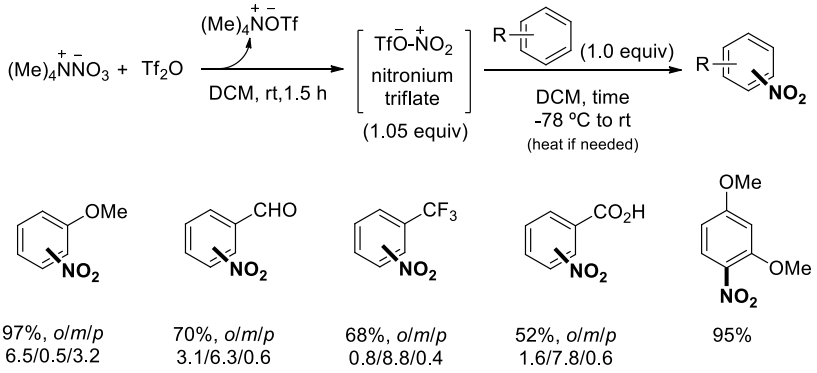
former examples cited, were applied to highly activated aromatic substrates, mostly phenols and heteroaromatic compounds.

Another type of nitrating salts, which present a higher organic character, are alkyl nitrates.[90] For example, alkylammonium nitrates, in the presence of triflic anhydride *in situ* form nitronium triflate, which is a very powerful nitrating agent.[91] Following this method, in 2003, Schackelford[91a] nitrated a wide range of aromatic and heteroaromatic compounds bearing both electron-donating and -withdrawing substituents. To a cooled suspension of nitronium triflate (1.05 equiv) at -78 ºC was added dropwise the corresponding aromatic derivative (1.0 equiv) dissolved in dry DCM. The solution was slowly warmed up to rt and heated when needed, yielding the corresponding nitro derivatives in moderate to excellent yields (52-97%). Regretfully, in the case of monosubstituted benzene derivatives, low selectivity was achieved, as various isomers were obtained in all the cases (Scheme 2.13).

Lett. **2006**, *47*, 6879. c) [$AgNO_3/BF_3$]; G. A. Olah, A. P. Fung, S. C. Narang, J. A. Olah, *J. Org. Chem.* **1981**, *46*, 3533.

[90] Different combinations of alkyl nitrates with strong Lewis acids have been described for the nitration of aromatic compounds (even those bearing electron-withdrawing substituents). For selected exampes, see: a) H. Feuer, H. Friedman, *J. Org. Chem.* **1975**, *40*, 187. b) H. Feuer, J. P. Lawrence, *J. Org. Chem.* **1972**, *37*, 3662.

[91] a) S. A. Schackelford, M. B. Anderson, L. C. Christine, T. Goetzen, M. C. Guzman, M. A. Hananel, W. D. Kornreich, H. Li, V. P. Pathak, A. K. Rabinovich, R. J. Rajapakse, L. K. Truesdale, S. M. Tsank, H. N. Vazir, *J. Org. Chem.* **2003**, *68*, 267. b) C. M. Adams, C. M. Sharts, S. A. Schackelford, *Tetrahedron Lett.* **1993**, *34*, 6669. For a recent example, see: c) G. Aridoss, K. K. Laali, *J. Org. Chem.* **2011**, *76*, 8088.



Scheme 2.13

- ***Ipso*-nitration**

When a group other than "H" is displaced from an aromatic ring, the nitration is called "*ipso* nitration" (from the Latin *ipso* = itself). This type of aromatic substitution was first referred to as *ipso*-substitution by Perrin and Skinner in 1971.[92] In this context, different *ipso*-nitration protocols have been presented during the past years as alternative pathways for synthesizing nitroaromatic compounds in a regiocontrolled manner, avoiding the undesired *ortho*/*meta*/*para* nitration regioisomeric mixtures.

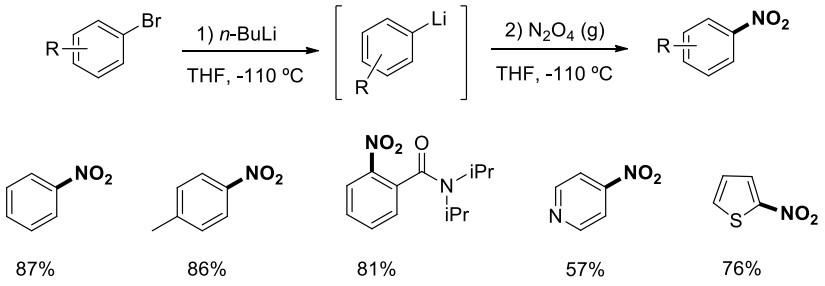
➢ ***Nitrodemetallation reactions***

The nitration of aryl and heteroaryllithium species with N_2O_4 was reported in 1997 by Eaton.[93] Treatment of the corresponding arene or bromo-arene with an organolithium reagent, generated the corresponding active aryllithium intermediate which subsequent treatment with gaseous N_2O_4 at low temperatures, effectively nitrated both electron-rich and electron-poor aromatic compounds in high yields

[92] C. L. Perrin, G. A. Skinner, *J. Am. Chem. Soc.* **1971**, *93*, 3389.

[93] K. Tani, K. Lukin, P. E. Eaton, *J. Am. Chem. Soc.* **1997**, *119*, 1476.

(57-87%), Scheme 2.14.[94] Although this reaction works well for aryl- and heteroaryl-lithium species, rigorous anhydrous and very low temperatures (typically below -100 ºC) conditions are required.[95]



Scheme 2.14

An efficient alternative to these nitrodemetallation reactions is the employment of aryl boronic acids which are commercially available, non-toxic and stable solid compounds.[96,97] It was in 2000 when Olah reported the first *ipso*-nitration of arylboronic acids with Crivello´s reagent (ammonium nitrate and trifluoroacetic

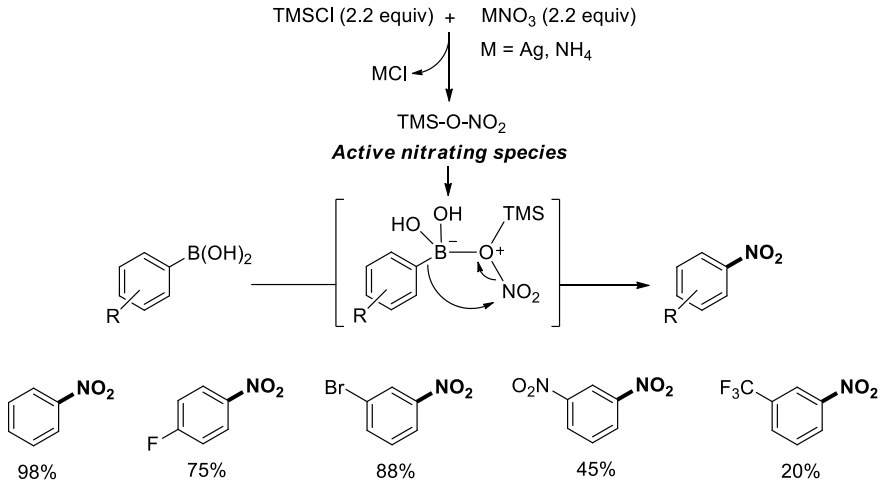
[94] Much more recently, Gribble followed this strategy for the nitration of *N*-Boc and *N*-(phenylsulfonyl)indoles, see: J. Jiang, G. W. Gribble, *Tetrahedron Lett.* **2002**, *43*, 4115.

[95] Analogously, the nitration of heteroarylstannanes with nitromethane and N_2O_4 has been reported in the literature. For selected examples, see: a) V. Fargeas, F. Favresse, D. Mathieu, I. Beaudet, P. Charrue, B. Lebret, M. Piteau, J. –P. Quintard, *Eur. J. Org. Chem.* **2003**, 1711. b) F. Favresse, V. Fargeas, P. Charrue, B. Lebret, M. Piteau, J. –P. Quintard, *J. Organomet. Chem.* **2000**, *598*, 187. However, the toxicity of these materials make their application very limited. For a selected textbook on Tin chemistry, see: c) A. G. Davies, M. Gielen, K. H. Pannell, E. R. T. Tieknink, *Tin Chemistry, Fundamentals, Frontiers and Applications*, Wiley & Sons, Chichester, United Kingdom, **2008**.

[96] D. G. Hall, *Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine*, Wiley-VCH, Weinheim, **2005**.

[97] Nitrodecarboxylation has also been reported as an alternative of *ipso*-nitration. However this approach has not been widely applied. For a selected article regarding the nitrodecarboxylation of α,β-unsaturated carboxylic acids and highly activated methoxy substituted benzoic acids using HNO_3, see: a) J. P. Das, P. Sinha, S. Roy, *Org. Lett.* **2002**, *4*, 3055. For a review on decarboxylative coupling reaction, see: b) N. Rodríguez, L. J. Goossen, *Chem. Rev.* **2011**, *40*, 5030.

anhydride),[98] in which, mono or di-nitrated arenes were obtained depending on the concentration. Improving this methodology, in 2004 Olah presented a highly selective, more simple and convenient protocol for the nitration of aryl boronic acids with a nitrate salt (silver or ammonium, 2.2 equiv) and clorotrimethylsilane (TMSCl, 2.2 equiv).[99] The reaction tolerated halogens as well as electron-withdrawing substituents, although the latter ones presented a moderate reactivity (20-45%). The authors proposed an electronic interaction between the boronic acid and the *in situ* generated active nitrating species, TMS-O-NO_2, due to the oxophilicity of the boron, as represented in Scheme 2.15.



Scheme 2.15

After this novel reactivity, several methods have appeared in the literature for the *ipso*-nitration of aryl boronic acids. Other nitrate salts, such as $Bi(NO_3)_3/K_2S_2O_8$[100] and

[98] S. Stefan, S. Jurgen, G. K. S. Prakash, N. A. Petasis, G. A. Olah, *Synlett.* **2000**, 1485.

[99] G. K. S. Prakash, C. Panja, T. Mathew, V. Surampudi, N. A. Petasis, G. A. Olah, *Org. Lett.* **2004**, *6*, 2205.

[100] a) S. Manna, S. Maity, S. Rana, S. Agasti, D. Maiti, *Org. Lett.* **2012**, *14*, 1736. b) R. R. Yadav, R. A. Vishwakarma, S. B. Bharate, *Tetrahedron Lett.* **2012**, *53*, 5958.

$Fe(NO_3)_3{\cdot}9H_2O$,[101] *tert*-butyl nitrite[102] and copper-catalyzed strategies[103] have efficiently been used in the nitration of a wide number of aromatic and heteroaromatic compounds, with both electron-donating and -withdrawing substituents.

- ***Cross-coupling reaction with aryl halides and pseudohalides***

  - *Copper catalyzed ipso-nitration with aryl halides*

In 2005, Saito reported a novel method for the copper-catalyzed *ipso*-nitration of aryl halides, using nitrite salts such as *n*-tetrabutylammonium nitrite (n-Bu_4NNO_2) (1.2 equiv) and copper bronze/DMEDA (*N*,*N*-dimethylethylenediamine) based catalytic system (5 and 10% mol respectively).[104] Although no mechanistic studies are described, an Ullman-type pathway is proposed.[105] While good yields were achieved for electron-rich aromatic rings, those substrates bearing electron-withdrawing groups presented lower reactivity. It is worth mentioning that the method

[101] M. Jiang, H. Yang, Y. Li, Z. Jia, H. Fu, *RSC Adv.* **2013**, *3*, 25602.

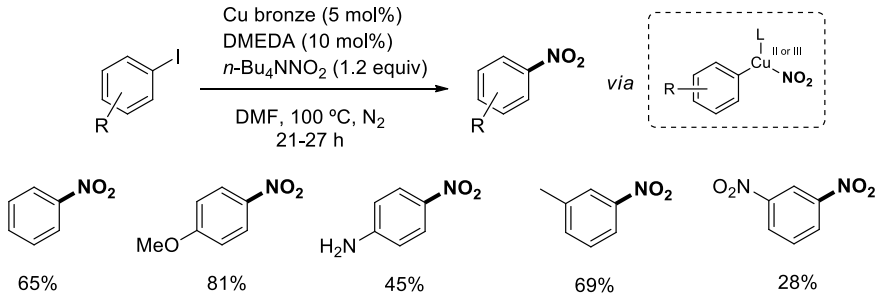
[102] a) X. -F. Wu, J. Schranck, H. Neumann, M. Beller, *Chem. Commun.* **2011**, *47*, 12462. Although the use of TBN as nitrating agent has become more popular during the last years, just a few examples are reported in the literature where this nitro source is used. For the nitration of phenols with TBH, see: b) D, Koley, O. C. Colón, S. N. Savinov, *Org. Lett.* **2009**, *11*, 4172. For the nitration of olefins with TBH, see: c) D. Hirose, T. Taniguchi, *Beilstein J. Org. Chem.* **2013**, *9*, 1713. d) S. Maity, T. Naveen, V. Sharma, D. Maiti, *Org. Lett.* **2013**, *15*, 3384. e) T. Taniguchi, A. Yajima, H. Ishibashi, *Adv. Synth. Catal.* **2011**, *353*, 2643. For a recent nitro-carbocyclization of activated alkenes, see: f) T. Shen, Y. Yuan, N. Jiao, *Chem. Commun.* **2014**, *50*, 554. TBN is potential hazardous due to its known highly exothermic decomposition (1200 J/g) at elevated temperatures (above 110 ºC), see: g) P. G. Urben, *Bretherick´s Handbook of Reactive Chemical Hazards*, Elsevier, Amsterdam, **2007**.

[103] a) G. Yan, L. Zhang, J. Yu, *Lett. Org. Chem.* **2012**, *9*, 133. b) H. Yang, Y. Li, M. Jiang, J. Wang, H. Fu, *Chem. Eur. J.* **2011**, *17*, 5652.

[104] S. Saito, Y. Koizumi, *Tetrahedron Lett.* **2005**, *46*, 4715.

[105] Oxidative addition of a Cu^0 or Cu^I species to the carbon–halogen bond generates a Cu^{II} or Cu^{III} intermediate. The subsequent halogen-nitrite exchange and final reductive elimination forms the nitro compound regenerating the Cu^0 or Cu^I system.

tolerated a *para*-NH_2 group, yielding the corresponding *para*-nitro aniline (45%) (Scheme 2.16).[106]



Scheme 2.16

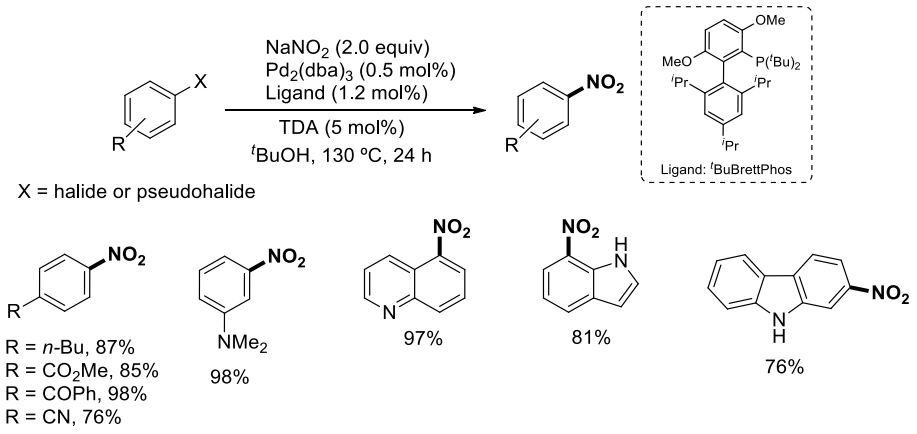
- *Palladium catalyzed ipso-nitration with aryl halides and pseudohalides*

In 2009, Buchwald reported one of the most adaptable and convenient protocols for the *ipso*-nitration of aromatic and heteroaromatic substrates.[107] A wide number of aromatic and heteroaromatic halides and pseudohalides bearing both electron-donating and -withdrawing substituents were selectively nitrated with $NaNO_2$ (2.0 equiv) in high yields (74-99%) by using a $Pd_2(dba)_3$/phosphine ligand/phase transfer catalyst ,TDA [tris-(3,6-dioxaheptyl)amine] system. Interestingly, when the amount of TDA was increased, the conversion to the product decreased, probably because higher concentrations of nitrite in solution could oxidize Pd^0 or the ligand,

[106] More recently, other Cu-catalyzed protocols have been reported in the literature for the i*pso*-nitration of halogenated aromatics. For a microwave accelerated protocol, see: a) P. LaBeaume, M. Placzek, M. Daniels, I. Kendrick, M. McNeel, R. Afroze, A. Alexander, R. Thomas, A. E. Kallmerten, G. B. Jones, *Tetrahedron Lett.* **2010**, *51*, 1906. For a Cu-ligand free nitration of a wide range of iodoarenes, bromoarenes and heterocyclic haloarenes, bearing both electron-withdrawing and -donating substituents, see: b) P. J. A. Joseph, S. Priyadrshini, M. L. Kantam, H. Maheswaran, *Tetrahedron Lett.* **2012**, *53*, 1511.

[107] a) B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 12898. See also: b) F. Barrios-Landeros, B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 8141. c) T. Ikawa, T. E. Barder, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 13001.

Scheme 2.17. This postulate was corroborated by running the reaction with a soluble source of nitrite (tetrabutylammonium nitrite), where just a 2% of the expected nitro derivative was obtained.



Scheme 2.17

All these alternatives, proposed in the *ipso*-nitration of arenes, circumvented regioselectivity problems in a very elegant way. Nonetheless, the necessity of substrate prefunctionalization, as well as, in some cases reactivity limitations to substrates bearing electron-withdrawing groups, encouraged the research of greener and more general nitration protocols.

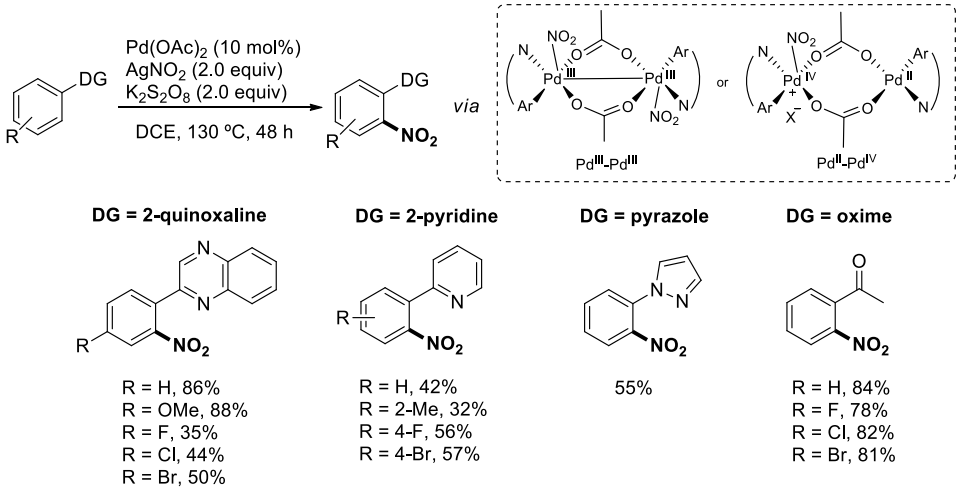
- ***C–H metal-catalyzed ortho nitration of arenes with directing groups***

In 2010, Xu reported the first palladium-catalyzed chelation-assisted *ortho*-nitration of aza-arenes using $AgNO_2$ as nitrating agent.[108] Among the different nitrogen-containing heteroaromatic donors surveyed as directing groups, 2-quinoxaline resulted the most effective (Scheme 2.18). Electron-rich aryl rings, generally afforded the *ortho*-nitration products in moderate to good yields (76-93%), while electron-deficient substrates provided lower yields (35-51%). Related *N*-donors

[108] Y. K. Liu, S. –J. Lou, D. –Q. Xu, Z. –Y. Xu, *Chem. Eur. J.* **2010**, *16*, 13590.

tethered aromatic substrates, such as 2-arylpyridines, benzo[*h*]quinoline, 2-arylpyrazoles and even *O*-methyl oximes were also suitable substrates for *ortho*-nitration, albeit with lower yields (32-67%). In spite of substrate limitations, this new approach to nitroarenes shows remarkable features such as high mono-nitration selectivity and regiospecific nitration at the *ortho* position relative to the nitrogen donors, regardless of the effect of other functionalities. However, poor regioselectivity was achieved with unsymmetrical aromatic rings.

On the basis of an observed inhibition of the reaction in the presence of TEMPO as radical scavenger, the authors proposed a silver-mediated radical mechanism ($AgNO_2 \rightarrow NO_2^{\bullet}$), involving Pd^{II}/Pd^{III} or Pd^{II}/Pd^{IV} catalytic cycles, under oxidative conditions ($K_2S_2O_8$, 2.0 equiv), upon initial rate-determining *ortho* cyclometallation step.

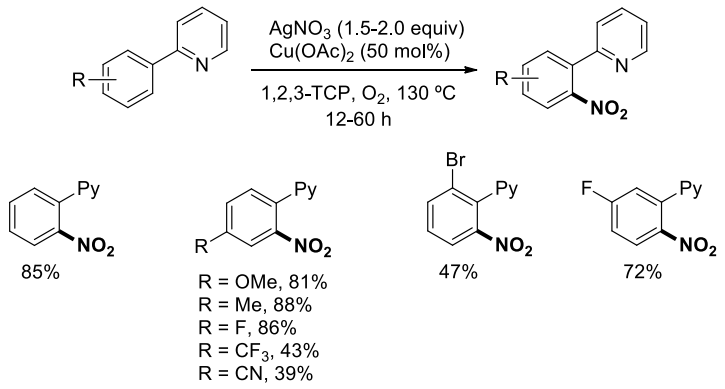


Scheme 2.18

Soon after Pd-catalyzed Xu´s protocol, Liu and co-workers reported a new approach to *ortho*-regioselective aromatic nitration of the same type of derivatives, namely aromatic substrates containing a nitrogen heteroaryl unit as directing group, such as 2-pyridyl, 2-pyrimidyl, 2-thiazoyl or 2-pyrazoyl groups, using $AgNO_3$ as nitro

source (1.5-2.0 equiv).[109] Distinctive advantages of this protocol include the use of $Cu(OAc)_2$ as promoter, yet in a high loading (50 mol%) and dioxygen (O_2, 1 atm) as terminal oxidant, thus avoiding the use of expensive and toxic Pd-catalysts and the waste generation derived from the stoichiometric use of oxidant salts such as $K_2S_2O_8$. However, the low environmentally friendly polyhalogenated alkane 1,2,3-trichloropropane (1,2,3-TCP) was required as solvent to achieve high conversion in the nitration.[110]

This protocol was very well-suited for 2-arylpyridines but other related heteroaryl directing groups provided relatively lower yields and longer reaction times. As in the former Pd-catalyzed nitration, the reaction rate was accelerated by the presence of electron-donating substituents on the aryl ring.



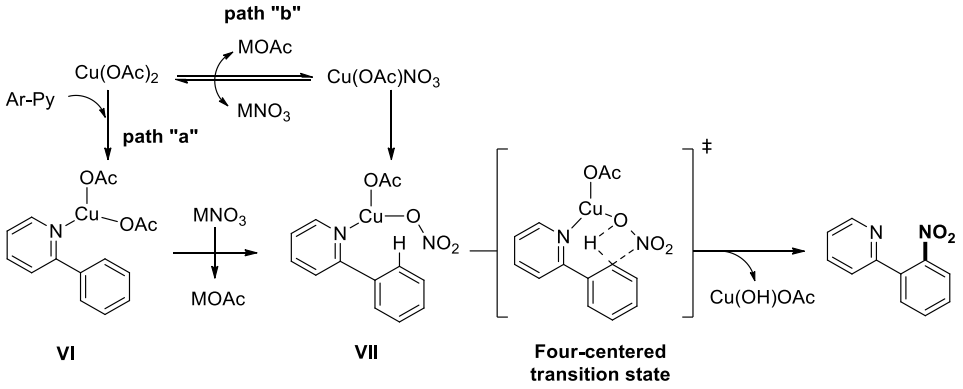
Scheme 2.19

An investigation of the reaction mechanism, including the exploration of alternative nitro-sources, revealed that both nitronium ion and $NO_2^{\bullet}$ free radical (resulting from decomposition of $AgNO_3$) can be excluded as the reactive NO_2

[109] L. Zhang, Z. Liu, H. Li, G. Fang, B. –D. Barry, T. A. Belay, X. Bi, Q. Liu, *Org. Lett.* **2011**, *13*, 6536.

[110] 1,2,3-TCP may act as an oxidant or proton donor like other chlorinated alkanes. For selected references, see: a) L. Ilies, S. Asako, E. Nakamura, *J. Am. Chem. Soc.* **2011**, *133*, 7672. b) L. Jin, J. Xin, Z. Huang, J. He, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 9607.

species. Nevertheless, the discovery that $Cu(NO_3)_2{\cdot}H_2O$ alone acted as an efficient nitrating agent provided an important clue to the reaction mechanism because the *in situ* decomposition of $CuNO_3X$ (X may be nitrate or other anion) could be the pathway producing the reacting NO_2 species involved in the C–H *ortho* nitration. Finally, inhibition of the nitration by a free radical scavenger such as TEMPO, indicated that the reaction likely proceeds through a radical mechanism. On the basis of these evidences, the authors proposed a plausible reaction mechanism initiated by formation of Cu^{II}-nitrate complex **VII**, formed by AcO^-/NO_3^- ion exchange, either from the complex **VI** (path “a”) or between $Cu(OAc)_2$ and a nitrate salt (path “b”). Subsequently, *ortho* nitration might take place through a four-centered transition state in which cleavage of C–H and N–O bonds, formation of O–H and C–N bonds, and transfer from carbon to oxygen occurred simultaneously.



Scheme 2.20

2.2.4. Nitration of anilines

Traditionally, certain aniline derivatives have been nitrated in strongly acidic media.[111,112] Due to the basic properties of these compounds, under these acid reaction conditions the ammonium salt (highly electron-withdrawing, *meta* directing) is formed.

For example, in 2007, Zhang reported a very illustrative protocol where aniline, *N*-methyl aniline and *N,N*-dimethyl aniline-nitric salts were nitrated.[113] Reaction of the corresponding aniline with stoichiometric HNO_3 in a TBME/THF mixture at 0 ºC for 1 h, generated the corresponding anilinium nitrate salt. Subsequent dropwise addition of the preformed salt in DCM to concentrated sulphuric acid at 0 ºC resulted in the formation of the nitro compounds. As the protonated amino group is strongly deactivated, activating groups already present on the aromatic rings dictated the regioselectivity of the reaction. For instance, the *N,N*-dimethyl-3-toluidine selectively yielded the *para*-nitro derivative (**XII**, 94%, *ortho* to the methyl group) without detecting any *meta*- nitro derivative, which corroborates that the regioselectivity of the reaction is dictated by the effect of activating *ortho-para* directing groups. In the absence of activating groups, mixtures of regioisomers, mainly *meta*- and *para*-isomers were formed. To illustrate this, aniline nitrate salt resulted in mixture of the corresponding *ortho*/*meta*/*para* nitro derivatives (**VIII**, 93%, ratio 0.3/5.0/4.7).

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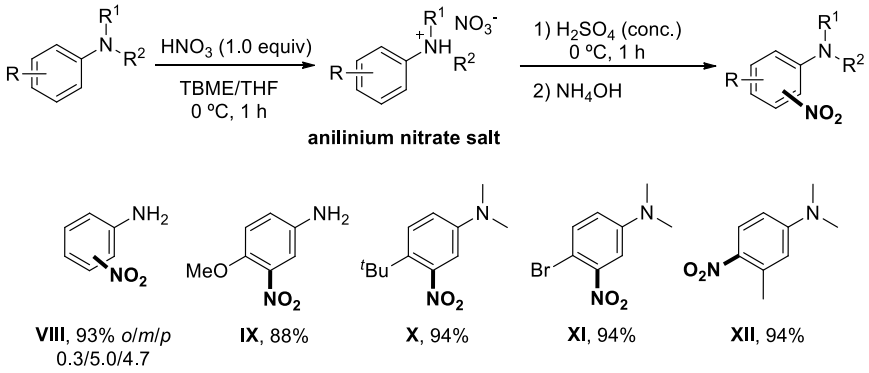
[111] F. C. Blanck, *The Nitration of Aniline and Certain of its Derivatives*, Kessinger Legacy Reprints, **1908**.

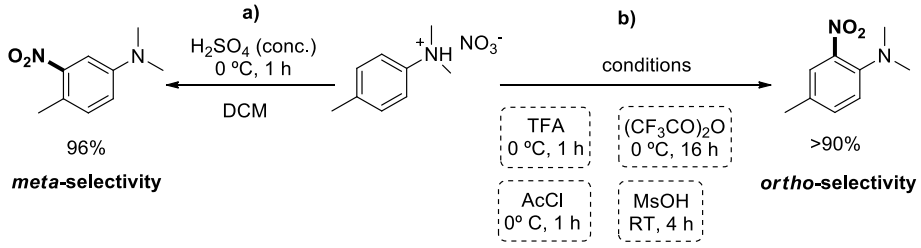
[112] Strong acidic methodologies exhibit harsh reaction conditions, lack of regioselectivity, formation of different by-products such as polynitrated arenes, *N*-nitroanilines or *N*-nitrosoanilines and scope limitations towards electron-withdrawing substituents. *N*-nitroanilines can undergo the nitramine rearrangement under strong acid conditions forming the corresponding nitroaniline derivatives. *N*-nitrosoanilines can undergo the Fischer-Hepp rearrangement under an acid catalyzed isomerization yielding the *para*-nitrosoaniline, see: O. Fischer, E. Hepp, *Ver Deutsch Chem. Ges.* **1886**, *19*, 2991.

[113] P. Zhang, M. Cedilote, T. P. Cleary, M. E. Pierce, *Tetrahedron Lett*. **2007**, *48*, 8659.



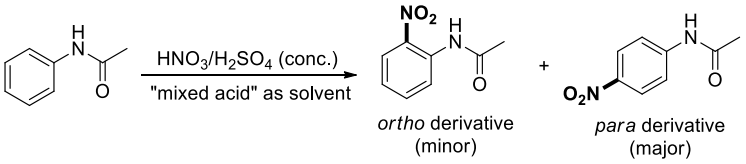
Scheme 2.21

Zhang also corroborated that the regioselectivity of the nitration of anilinium salts is extremely dependent on the reaction conditions. For example, when *N,N*-dimethyl-*p*-toluidine nitrate salt (with the *para*-position blocked with the methyl substituent) was subjected to further reaction in concentrated H_2SO_4, the *meta*- nitrated derivative (relative to -NMe_2) was selectively generated in high yield (96%, Scheme 2.22a). However, the selectivity of the reaction could be switched by changing the reaction conditions. By way of example, using other reagents as solvent, such as TFA, $(CF_3CO)_2O$, AcCl and MsOH, the reaction yielded cleanly the *ortho*-nitro aniline derivative in high yields (typically, >90%, see Scheme 2.22b).



Scheme 2.22

One of the most common and extended methods for the nitration of anilines is their derivatization to acetanilides, which under “mixed-acid” reaction conditions yields a mixture of *para*- (major) and *ortho*- (minor) nitro derivatives.[36c,111] An advantage of this transformation is that once the nitro moiety is introduced in the aromatic ring, the acetyl group can easily be removed under acidic or basic conditions.[114]

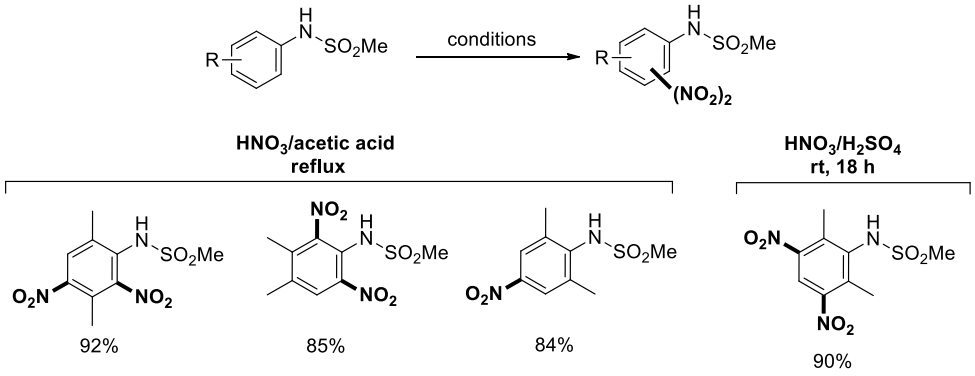


Scheme 2.23

The nitration of methanesulfonamides, which are excellent *ortho*/*para* directing groups for electrophilic aromatic substitution, also exhibited a significant dependence towards the reaction conditions, as reported by Hanson.[115] The nitration of methyl-substituted methanesulfonamides afforded the *ortho*/*para*-di-nitro derivatives in high yields (84-92%), using a refluxing nitric/acetic acid mixture. However, this regiochemistry was inverted by a mixture of nitric/sulphuric acid where the *meta*-di-nitro derivative was isolated as the only product (90%), (Scheme 2.24).

[114] For an *ortho*-selective nitration of acetanilides following the *Kyodai* nitration (NO_2/O_3) in chloroform, see: H. Suzuki, T. Ishibashi, T. Murashima, K. Tsukamoto, *Tetrahedron Lett.* **1991**, *32*, 6591.

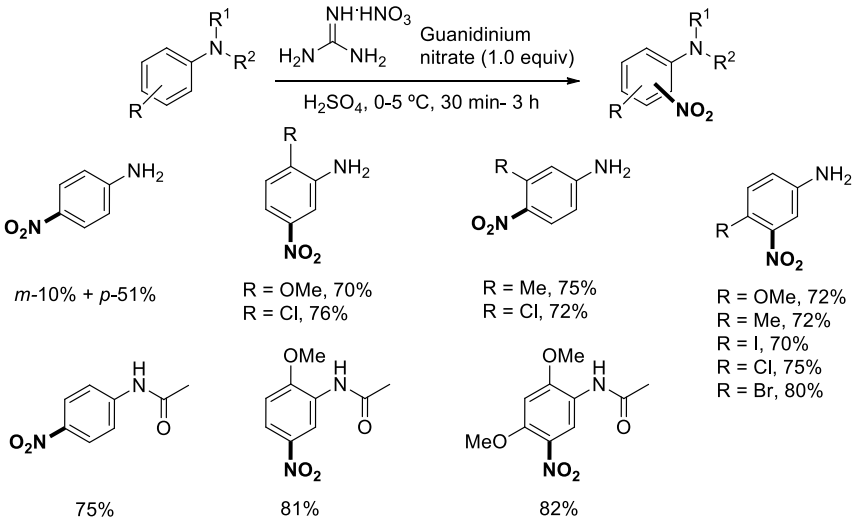
[115] S. Al-Khafaji, N. Cardinale, J. R. Hanson, *J. Chem. Research*, **2003**, 383.



Scheme 2.24

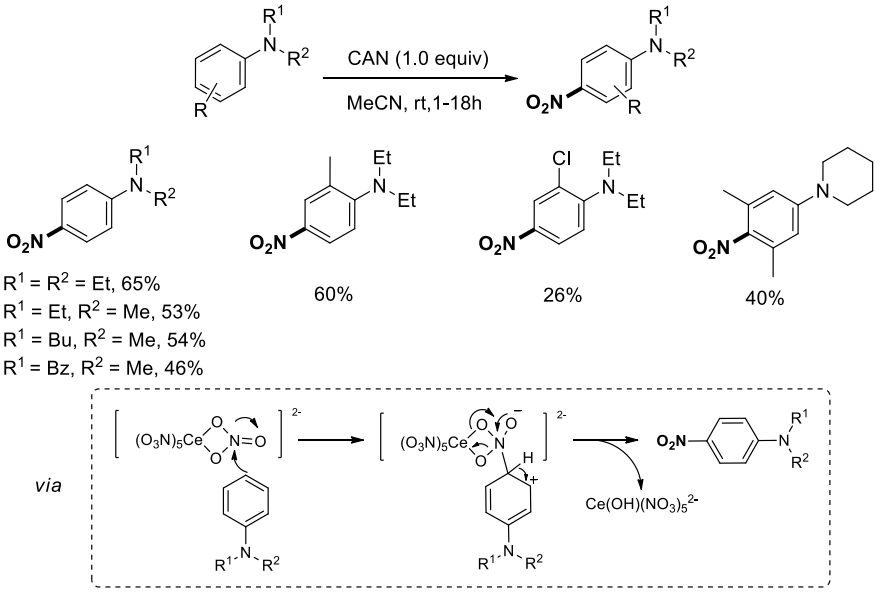
Other methods with different nitro sources have also been reported for the nitration of aniline derivatives using acidic solvents. For example, in 2004, Ramana reported a novel methodology where anilines were efficiently nitrated with guanidinium nitrate (1.0 equiv) in concentrated H_2SO_4 as solvent at low temperatures (0-5 ºC) and short reaction rates (30 min to 3 h).[116] The regioselectivity of the reaction was dictated by the presence of activating groups, generally yielding the *ortho*- or *para*-nitro derivatives with respect to the cited substituents (61-81%). Although this alternative is applicable to a wide range of activated and halogen-containing aniline derivatives, the use of sulphuric acid as solvent generates an undesirable large amount of acidic waste, (Scheme 2.25).

[116] M. M. V. Ramana, S. S. Malik, J. A. Parihar, *Tetrahedron Lett.* **2004**, *45*, 8681.



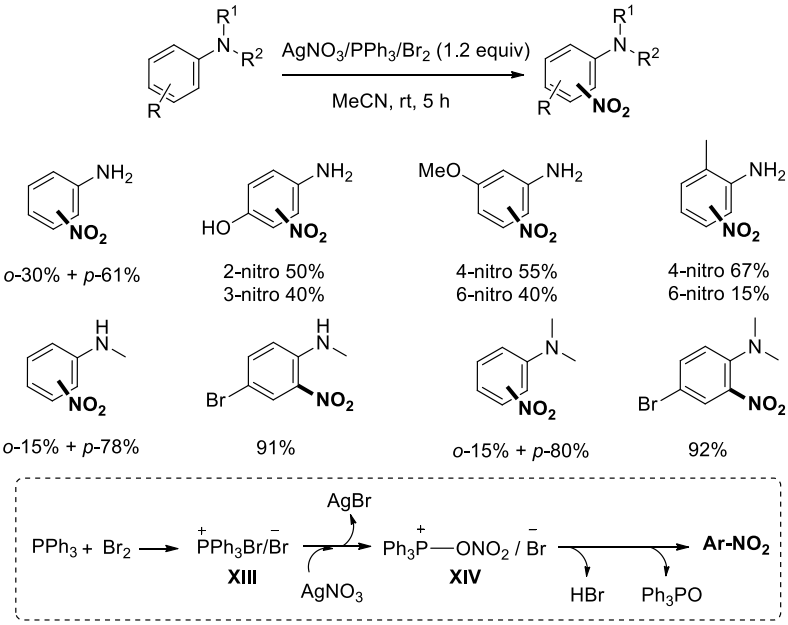
Scheme 2.25

In 2005 Xi developed a new method for the *para*-regioselective nitration of *N*,*N*-dialkylanilines.[88a] In this work, CAN (ceric ammonium nitrate) (1.0 equiv) acts as a carrier of nitronium species and the electrophilic nitration reaction occurs through a molecular rearrangement with metal containing species. Although this approach provides a wide range of differently *N*-alkyl-substituted aniline derivative (Me, Et, *n*-Bu, Bz) under mild reaction conditions (MeCN as solvent at room temperature), the substitution in the aromatic ring is very limited, moderate yields are achieved (26-65%) and a stoichiometric amount of cerium salt waste is generated, Scheme 2.26.



Scheme 2.26

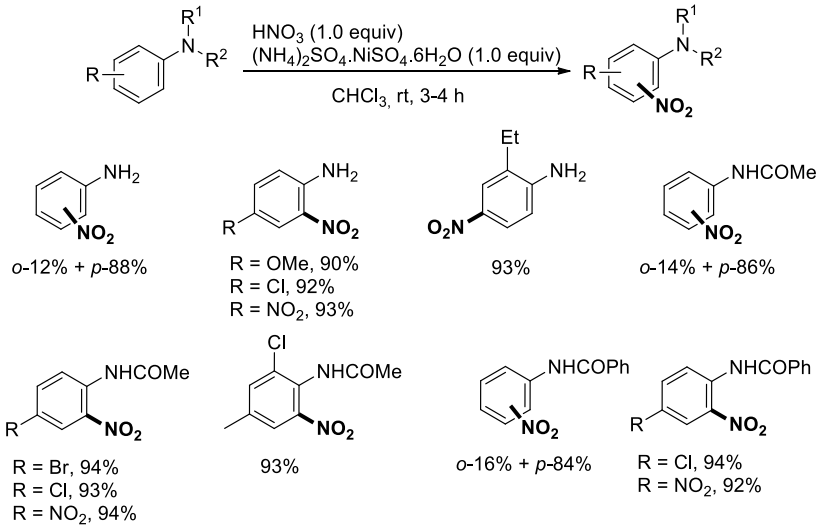
Iranpoor reported in 2006 the application of $AgNO_3/PPh_3/Br_2$ (1.2 equiv) as a novel protocol for the nitration of anilines.[89b] The reaction of PPh_3 with Br_2 generates the phosphonium intermediate **XIII**, which evolves to **XIV** (triphenylphosphonium nitrate) with concomitant precipitation of AgBr. Electrophilic addition of intermediate **XIV** to the aromatic system yields the expected nitro compounds and triphenylphosphine oxide, (Scheme 2.27). This procedure represents an alternative to the use of mixed acids and operates under mild reaction conditions (MeCN as solvent, rt, 5 h). It is also remarkable its tolerance to halogen-containing aniline derivatives (*para*-Br-*ortho*-nitro, 91%). Nonetheless, it shows a low regioselectivity (mixtures of nitro compounds are generated) and does not work for strongly deactivated aromatic systems.



Scheme 2.27

In spite of the availability of alternative nitrating agents, the use of HNO_3 remains to be the top choice for commercial scale-up nitration processes. In this context, Rajanna reported in 2001 an ammonium nickel sulphate mediated nitration of a wide range of aniline derivatives using one equivalent of HNO_3.[117] This reaction proceeded rapidly at room temperature in chloroform for 3-4 h, allowing the corresponding mono-nitroderivatives in high yields and regioselectivities with both electron-donating and -withdrawing substituents, as well as halogen tolerance. It is very remarkable that *p*-nitroaniline, *p*-nitroacetanilide and *p*-nitrobenzanilide were elegantly converted into their corresponding 2,4-dinitroderivatives with excellent yields (>90%). However, the disposal of stoichiometric amounts of Ni salts made this approach limited from practical and environmental standpoints (Scheme 2.28).

[117] M. M. Ali, K. C. Rajanna, P. K. Saiparakash, *Synth. Commun.* **2001**, *31*, 1123.



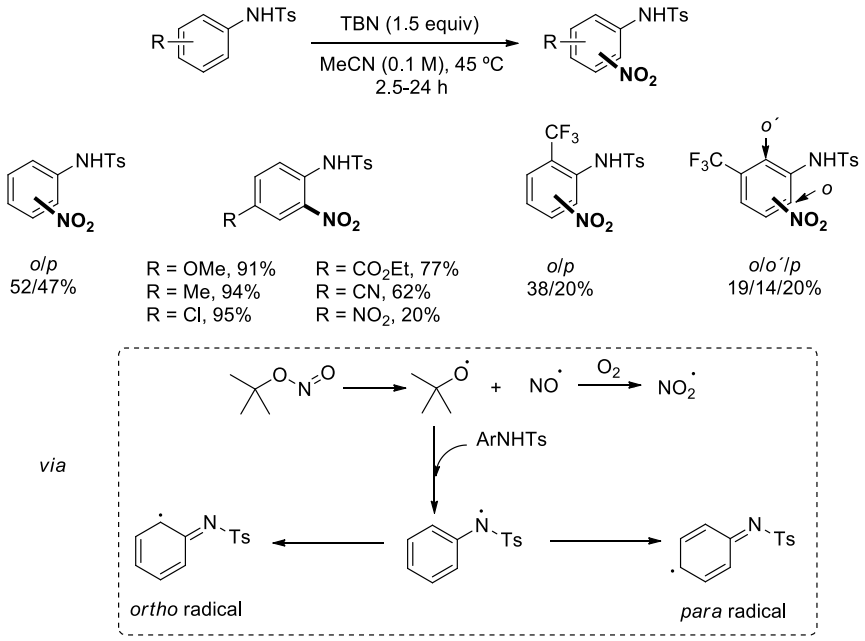
Scheme 2.28

Finally, during the development of our work, the group of Arns reported a protocol where a wide range of sulfonylated anilines (-NTs, -NMs, -NNs) were converted into their corresponding nitro derivatives using *tert*-butyl nitrite (TBN) as nitrating agent (1.5 equiv), in MeCN at 45 ºC.[118] Generally, electron-rich substrates were found to be more reactive (>90%), whereas moderate yields were achieved, even after prolonged reaction times (24 h), for strongly deactivated systems, bearing substituents such as $-CO_2Et$, -CN, $-CF_3$ or $-NO_2$ (20-77%). In the case of non-substituted anilines, mixtures of *ortho*- and *para*- nitrated species were observed, in approximately equal ratios. Those anilines bearing substituents in the *ortho*- or *meta*-positions resulted in a mixture of regioisomers as no regiocontrol could be achieved under reaction conditions (Scheme 2.29).

Additionally, inhibition of the nitration by a free radical scavenger, TEMPO, suggests that the reaction likely proceeds through a radical mechanism. Thermal

[118] B. Kilpatrick, M. Heller, S. Arns, *Chem. Commun.* **2013**, *49*, 514. For other publications regarding the use of TBN as nitrating agent and its chemical properties, see reference 104.

decomposition of TBN generates an alkoxyl radical, subsequent abstraction of the sulfonamide N–*H* proton, affording a nitrogen-based radical which delocalize onto the aromatic ring. Finally, the $NO_2^{\bullet}$ radical, generated by oxidation of NO with molecular oxygen, intercepts the aryl radical to give the expected nitro compounds. The lack of regioselectivity observed in non-substituted anilines was attributed to the delocalization of the aryl radical, being the more stable species those ones bearing the radical at the *ortho* and *para* positions.



Scheme 2.29

2.3. Aim of the project

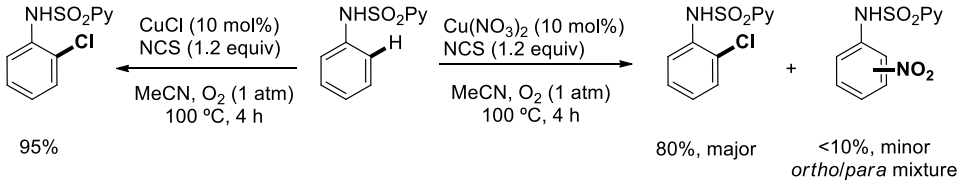
Despite the great advances made in the nitration of arene derivatives, there are still important challenges to be solved and room for innovation, mainly in increasing the efficiency and regiocontrol of the reaction and improving the current limited scope. For instance, by the time we started this project, just few methods had demonstrated to tolerate a wide range of substituents in the aromatic ring; the vast majority are restricted to electronically rich arenes, whereas strongly deactivated substrates generally show a very poor reactivity. In addition, the control of both regioselectivity and poly-substitution side reactions are some aspects that should be improved.

One of the most important issues to be solved is the lack of eco-friendliness that many of the reported protocols exhibit. Typically, the excess of mixed strong acid systems or the stoichiometric use of often expensive metal-nitrate salts in the reaction, are problematic and preclude the more general application of this reaction.

Therefore, there is great need for more general, practical, safe and green methods for the catalytic nitration of arenes. ***Compared to typical procedures that require disposal of significant amounts of strong acid, or metal wastes, a method using one equivalent of the inexpensive HNO_3 as nitrating agent and O_2 (1 atm) as terminal oxidant is ideal because no stoichiometric wastes are formed other than water***. In the specific case of nitration of aniline derivatives, the presence of a basic nitrogen can be problematic, often leading to untoward regioselectivities. Although most of the reported methods circumvent this problem by protecting the amino group as *N,N*-dialkyl or acetanilides, ***the structural scope of the reaction with regard to common N-protecting groups such as amides, carbamates or sulphonamides remains very limited.***

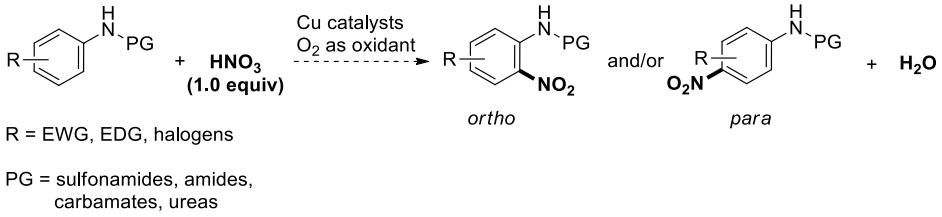
In line with Green Chemistry principles, as already mentioned in the introduction of the thesis, our research group has recently developed a methodology for the Cu-catalyzed *ortho* C–H halogenation of aniline derivatives under aerobic conditions.[31a] During the optimization studies of this reaction, we observed the

formation of traces (<10% yield) of nitroaniline derivatives (as a mixture of *ortho*/*para* regioisomers), accompanying the expected *ortho* halogenated aniline derivative when the copper(II) nitrate salt $Cu(NO_3)_2{\cdot}xH_2O$ was used as catalyst (10 mol%), (see Scheme 2.30 for a particular case).



Scheme 2.30

Given the importance of nitro aromatic compounds and the lack of reliable and general methods for the nitration of aniline derivatives under mild reaction conditions, available at the outset of this work, we envisioned a unique opportunity to develop an efficient Cu-catalyzed nitration protocol for aniline derivatives. Therefore, we planned to perform an in-depth study of this nitration reaction and the factors that control the reactivity, whose understanding we deemed essential for developing the derived catalytic system. The use of 1.0 equiv of HNO_3 as the "nitro" source in combination with O_2 as oxidant will be pursued as the ideal reaction conditions. The smooth reaction conditions should allow a wide structural scope with regard to both arene substitution and *N*-protecting groups (PG), (Scheme 2.31).

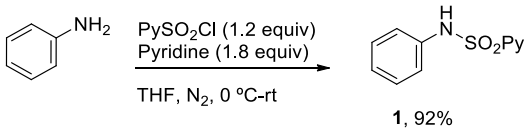


Scheme 2.31

2.4. Results and discussion[119]

2.4.1. Proof of concept: nitration of aniline 1 under stoichiometric copper

We started our research by studying the ability of $Cu(NO_3)_2 \cdot xH_2O$ in promoting nitration of *N*-(2-pyridyl)sulfonyl aniline **1**. As depicted in Scheme 2.32, *N*-(2-pyridyl)sulfonyl aniline **1** was readily prepared from commercially available aniline through a standard *N*-sulfonylation protocol with 2-pyridylsulfonyl chloride[120] in the presence of pyridine as base. The resulting sulfonamide **1** was isolated in excellent yield (92%) as a bench-stable solid.

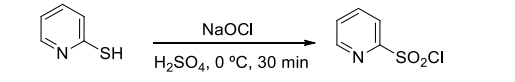


Scheme 2.32

Next, we attempted the prospective nitration of *N*-(2-pyridyl)sulfonyl aniline **1** using a stoichiometric amount of $Cu(NO_3)_2 \cdot xH_2O$ (1.0 equiv) under otherwise identical conditions to those used in the halogenation reaction, ($Cl_2CH_2CH_2Cl_2$, O_2 atmosphere at 130 ºC for 24 h).[31] Interestingly, full conversion towards nitroaniline derivatives ***o*-2** and ***p*-2** was achieved under these stoichiometric conditions, which were obtained in 94% combined yield without detecting side products from chlorination or polynitration

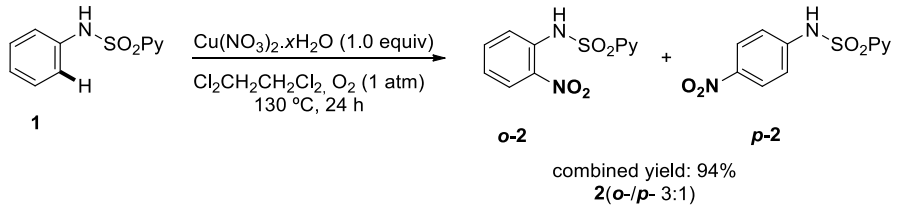
[119] This research Project was also supervised by Dr. Nuria Rodríguez.

[120] (2-Pyridyl)sulfonyl chloride is not commercially available and it needs to be prepared according to a literature procedure involving oxidation with sodium hypochlorite (commercial bleach) in concentrated sulphuric acid, see: S. Diltz, G. Aguirre, F. Ortega, P. J. Walsh, *Tetrahedron: Asymmetry* **1997**, *8*, 3559.



2-mercaptopyridine — 2-pyridylsulfonyl chloride

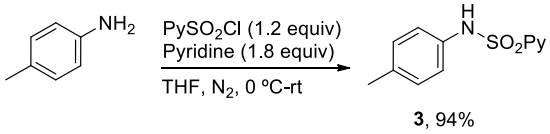
in the reaction mixture. Unfortunately, the reaction was not regioselective and a 3:1 mixture of *ortho*/*para* regioisomers was obtained (Scheme 2.33).



Scheme 2.33

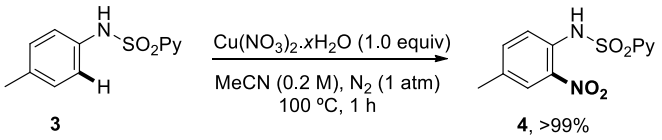
Even though this result was very encouraging, a stoichiometric amount of $Cu(NO_3)_2{\cdot}xH_2O$ was needed. Regretfully, the protocol described above also required 1,1,2,2-tetrachloroethane as solvent, which is toxic and industrially disfavoured, as well as 24 h heating at 130 ºC for reaction completion.

Consequently, we decided to embark on the development of a more efficient and environmentally benign protocol for selective nitration. In these optimization studies, to avoid the difficulties associated with the presence of regioisomeric mixtures in the analysis of the crude nitration mixtures by ^{1}H NMR, the *N*-(2-pyridyl)sulfonyl *p*-toluidine **3** was chosen as the model substrate, not only because the *para* position is blocked towards the nitration, but also because of the moderate activating effect of the methyl group. Compound **3** was prepared following the same *N*-sulfonylation procedure previously used for accessing the parent substrate **1** and it was obtained with similar yield (94%) as a stable and easy to handle solid (Scheme 2.34).



Scheme 2.34

First, it was deemed appropriate to find a solvent more attractive to industry. In this regard, acetonitrile is widely recognized as an industrial favoured solvent and, accordingly, it was our first choice as an alternative solvent.[121] We found that the copper-promoted nitration of *N*-(2-pyridyl)sulfonyl *p*-toluidine **3** occurs smoothly in acetonitrile to obtain the desired *ortho*-nitro product **4** quantitatively after 1 h at 100 ºC under N_2 atmosphere (Scheme 2.35). It is worth mentioning that the reaction proceeded cleanly and no di-nitrated species were detected in the ^{1}H NMR spectrum of the crude mixture.



3 **4**, >99%

Scheme 2.35

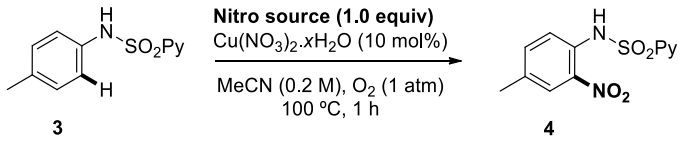
2.4.2. Development of a copper-catalyzed procedure for the nitration of anilines

- ***Use of nitrate and nitrite species as source of NO_2***

Next we focused on developing a catalytic, rather than stoichiometric (with respected to copper) protocol. In an initial attempt, we used inorganic nitrate salts such as KNO_3 and $AgNO_3$ as stoichiometric sources of NO_2 in the presence of 10 mol% of $Cu(NO_3)_2{\cdot}xH_2O$ and O_2 as external oxidant, but no nitration reaction was observed, recovering unaltered starting material **3** in both cases (Table 2.1, entries 1 and 2). When a more soluble salt, such as $(NH_4)NO_3$ was subjected to the reaction conditions, the desired nitrocompound **4** was detected in 12% ^{1}H NMR yield (entry 3). In sharp contrast, changing the nitro source to 1.0 equiv of *iso*-amyl nitrite resulted in almost full conversion of the starting material, affording compound **4** in 89% isolated yield (entry 4).

[121] For a recent study on the importance of MeCN in the pharmaceutical industry, see: I. F. McConvey, D. Woods, M. Lewis, Q. Gan, P. Nancarrow, *Org. Process Res. Dev.* **2012**, *16*, 612.

Table 2.1: Study of the nitrating agent



3 4

Entry	Nitrating agent	**4** Yield (%)[a]
1	KNO_3	0
2	$AgNO_3$	0
3	$(NH_4)NO_3$	12
4	*i*AmONO[b]	94 (89)[c]

[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *i*AmONO = *iso*-amyl nitrite; [c] Isolated yield

- ***Use of HNO_3 as nitrating species***

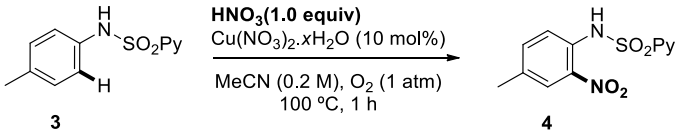
Despite the feasibility and significance of a nitration reaction of aniline derivatives under copper catalytic conditions and using dioxygen as terminal oxidant, we envisioned that the use of 1.0 equiv of the inexpensive HNO_3 as nitrating agent would represent a further significant improvement because, if feasible, the only stoichiometric by-product of the reaction would be water. In this regard, we wondered whether an anion exchange could occur between CuX_2 species and HNO_3, leading to the incorporation of nitrate ions into the Cu^{II} moiety. This would provide an advantage to HNO_3 (over *iso*-amyl nitrite) as nitrating agent by making the nitration process much more practical and economical.

To our delight, one equivalent of HNO_3 showed to be even more effective than *iso*-amyl nitrite under otherwise identical catalytic conditions, providing the expected *ortho*-nitro aniline derivative **4** in 95% isolated yield after 1 h at 100 °C (Table 2.2, entry 1). Full regioselectivity towards the *ortho* position was achieved, with neither

traces of *meta*-nitro derivatives nor polynitro species being detected in the reaction crude mixture.

Control experiments determined that nitro aniline derivative **4** is not produced in the absence of a copper catalyst (entry 2), and that the reaction requires aerobic conditions (1 atm of O_2) to enable catalyst turnover, since the reaction under inert atmosphere (1 atm of Ar) led to the recovery of the starting material **3** unaltered (entry 3). These results highlight the crucial role of both the catalyst and the oxidant in the nitration reaction.

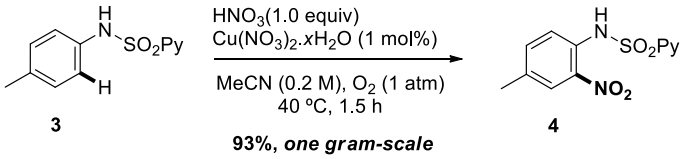
Table 2.2: Study of HNO_3 as nitrating agent



Entry	Conditions	**4** Yield (%)[a]
1	=	>98 (95)[b]
2	without Cu	<5
3	Argon atmosphere	<5

[a] Conversion yields by ^{1}H NMR spectroscopy; [b] Isolated yield.

From a synthetic practical standpoint, it is remarkable that this protocol allows simultaneous scale-up, lower catalyst loading, and lower temperature. For example a one-gram-scale nitration of sulfonamide **3** was performed with 1 mol% of $Cu(NO_3)_2{\cdot}xH_2O$ at 40 ºC for 1.5 h. Simple addition of water and removal of MeCN under vacuum caused precipitation of compound **4**, which was isolated in 93% yield upon filtration.



Scheme 2.36

2.4.3. Fine refinements of reaction parameters

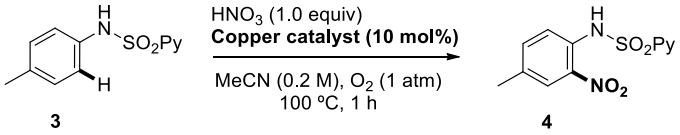
Although the reaction conditions already found were mild and efficient, we questioned whether it would be possible to achieve better reactivity by refining some reactions parameters.

- ***Influence of the nature of the copper precatalyst***

Having demonstrated the feasibility of anion exchange between CuX_2 salt and HNO_3, a brief screening of other Cu^{I} and Cu^{II} salts was carried out in the model reaction of *p*-toluidine derivative **3** under otherwise identical conditions to those in Table 2.2.

As shown in Table 2.3, changes in the nature of the copper salt, including variation in its oxidation state (I and II), appeared to have no influence on the reactivity, as identical reaction outcome was observed with catalyst precursors as different as $Cu(OAc)_2$ and CuCl. This observation adds additional weigh to the idea that facile anion exchange between HNO_3 and the copper salt must occur to enable reactivity under catalytic conditions.

Table 2.3: Study of the copper-based catalyst



3 **4**

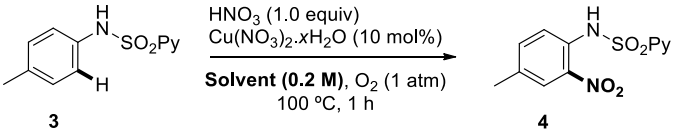
Entry	Copper catalyst	**4** Yield (%)[a]
1	$Cu(NO_3)_2{\cdot}xH_2O$	>98
2	$Cu(OAc)_2$	>98
3	CuCl	>98

[a] Conversion yields by ^{1}H NMR spectroscopy.

- ***Solvent screening***

A brief exploration of the influence of the nature of the solvent was also undertaken (Table 2.4). This study pointed towards an important role of polar solvents (regardless their protic or aprotic character) in the acceleration of the nitration process. For example, a polar acidic solvent such as acetic acid proved to be equally highly effective in the reaction as acetonitrile (Table 2.4, entries 1 and 2). In contrast, less polar solvents such as THF or dioxane presented a detrimental effect on reactivity, resulting in low conversions (24% and 12%, respectively, entries 3 and 4). In agreement with this trend, no reaction was observed even in less polar solvents such as toluene or DCE (<5% nitration product observed by ^{1}H NMR in the crude mixture, entries 5 and 6).

Table 2.4: Study of the solvent using HNO_3 as nitrating agent



Entry	Solvent	**4** Yield (%)[a]
1	AcOH	>98
2	MeCN	>98
3	THF	24
4	Dioxane	12
5	Toluene	<5
6	DCE	<5

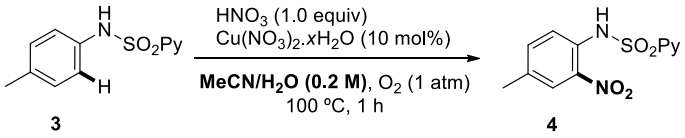
[a] Conversion yields by ^{1}H NMR spectroscopy.

The finding that polar protic solvents are perfectly suitable for the reaction, along with the tolerance to the presence of small amounts of water coming from the copper precatalyst [$Cu(NO_3)_2{\cdot}xH_2O$] as well as water formation as by-product in the nitration reaction, made us hypothesized about the possibility of performing the reaction in water as the reaction media.[122] Along this line, the influence of water on the catalytic activities was examined carrying out the model nitration of aniline derivative **3** in mixtures of MeCN/H_2O of different water content and determining the conversion of the reaction (measured by ^{1}H NMR) over the same time period (1 h), as illustrated in Figure 2.6.

The results suggest that although the reactivity is negatively influenced by the presence of water, a relative water content of up to 50% in the solvent mixture (i.e., MeCN/H_2O = 1:1) is well tolerated (91% conversion after 1 h). In contrast, a

[122] Note that this reaction proceeds smoothly with O_2 as terminal oxidant, in which no wastes are formed other than H_2O.

significant drop in conversion was observed for relative water content of above 50% (25% conversion in a 1:3 MeCN/H_2O mixture). This effect was attributed, at least partly, to a decrease in the solubility of the starting sulfonamide **3** as the water ratio increased.



% Water	% Conversion
0	>98
14	98
25	96
50	91
75	25
86	20
100	<2

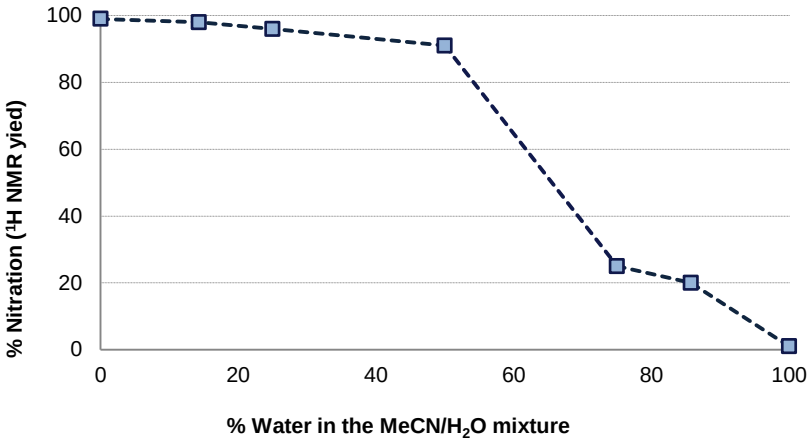


Figure 2.6

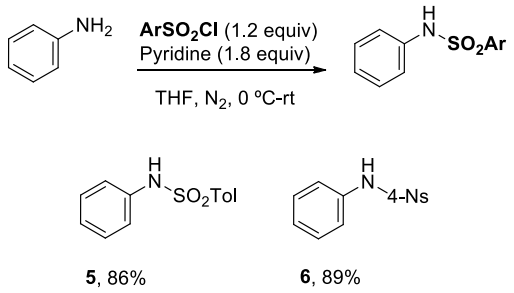
- ***Influence of the N-substitution on the reactivity and ortho/para regioselectivity***

With the optimized catalytic system in hand, we revisited the nitration of the parent aniline derivative **1**, without a blocking substituent at the *para*-position, to evaluate not only the versatility of this method, but also the influence of the nature of the *N*-protecting group on the reactivity and the *ortho*/*para*-regioselectivity. For this study, a varied set of aniline derivatives, having commonly used *N*-protecting groups

with different coordinating abilities, were synthesized by conventional protection protocols.

a) Sulfonamides

Anilines bearing *N*-sulfonyl protecting groups were prepared by the standard *N*-sulfonylation reaction with the corresponding sulfonyl chloride under identical conditions for the preparation of **1**. Thus, *N*-tosyl [Ts = (4-methylphenyl)sulfonyl] derivative **5** and *N*-nosyl [Ns = (4-nitrophenyl)sulfonyl] derivative **6** were isolated in good yields as stable solids (86% and 89%, respectively).

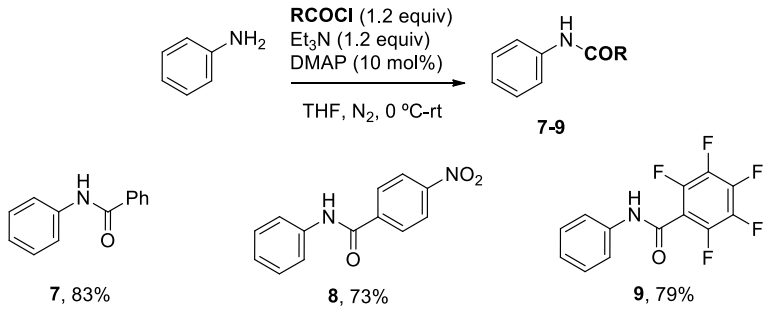


5, 86% **6**, 89%

Scheme 2.37

b) Amides

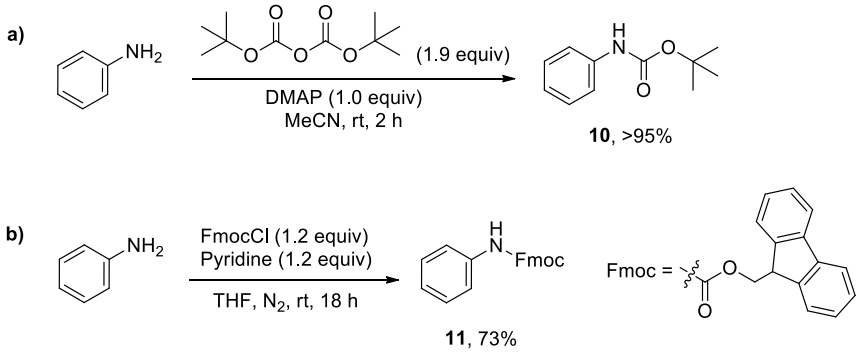
Amide-protected anilines **7**-**9** were synthesized in high yields (73-83%) by treatment of aniline with 1.2 equiv of the corresponding acid chloride in the presence of Et_3N as base and a catalytic amount of DMAP.



Scheme 2.38

c) Carbamates

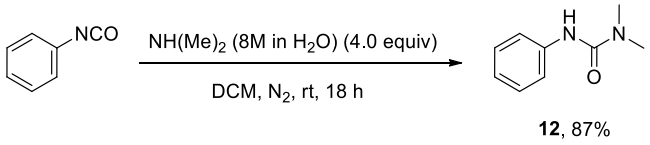
Anilines protected with easily removable carbamate groups were also considered as potential candidates for testing our nitration method. *N*-Boc aniline derivative **10** was prepared in excellent yield (>95%) by reaction of aniline with di-*tert*-butyl dicarbonate (Boc anhydride) and DMAP as catalyst (Scheme 2.39a). The corresponding *N*-Fmoc aniline **11** was synthesized in 73% yield using 9-fluorenylmethoxycarbonyl chloride (Fmoc chloride) (1.2 equiv) as *N*-acylating reagent and pyridine as base (1.2 equiv) (Scheme 2.39b).



Scheme 2.39

d) Ureas

N-acyl ureas, readily available from the corresponding isocyanates, have revealed as competent *ortho*-directing groups in a number of C–H functionalization reactions.[123] Therefore, these types of substrates are good candidates for testing our nitration protocol. The *N,N*-dimethyl urea **12** was efficiently prepared (87% yield) by reaction of phenylisocyanate with dimethylamine in DCM at room temperature, Scheme 2.40.



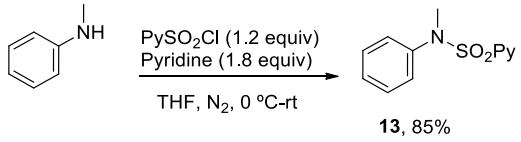
12, 87%

Scheme 2.40

e) N-alkylated anilines

The *N*-methyl-*N*-(2-pyridyl)sulfonyl aniline **13** was also prepared in order to study the effect of the free *NH* hydrogen in the sulfonamido moiety and therefore, test the tolerance of the reaction to *N*-alkyl substituents. Additionally, this evaluation can provide important clues about the reaction mechanism. The *N*-methyl sulfonamide **13** was prepared in 85% yield from commercially available methyl aniline, following the standard protocol for *N*-sulfonylation.

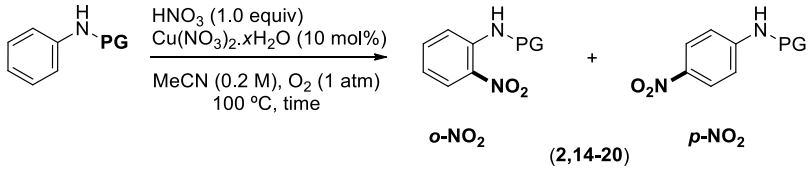
[123] For selected publications on the use of ureas as *ortho*-directing groups in C–H functionalization reactions, see: a) L. Wang, S. Liu, Z. Li, Y. Yu, *Org. Lett.* **2011**, *13*, 6137. b) J. Willwacher, S. Rakshit, F. Glorius, *Org. Biomol. Chem.* **2011**, *9*, 4736. c) T. Nishikata, A. R. Abela, S. Huang, B. H. Lipsbutz, *J. Am. Chem. Soc.* **2010**, *132*, 4978. d) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2009**, *48*, 1830.



Scheme 2.41

In order to compare the nitration rate and possible variations in regioselectivity, the different *N*-protected anilines (**5-13**), along with aniline **XV** and methyl aniline **XVI** were examined under our optimized nitration conditions [HNO_3 (1.0 equiv), $Cu(NO_3)_2{\cdot}xH_2O$ (10 mol%), using molecular oxygen as the final oxidant, in acetonitrile as solvent at 100 °C]. The results are summarized in Table 2.5.

Table 2.5: Optimization of the *N*-protecting group



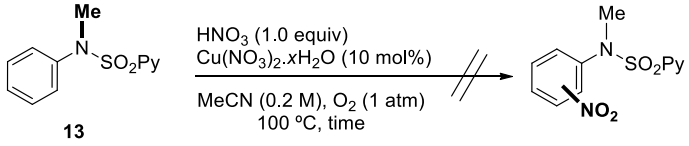
Entry	PG	*o:p* ratio[a]	*o*-NO_2 (%)[b]	*p*-NO_2 (%)[b]
1	NH_2 (**XV**)	-[c]	-	-
2	NHMe (**XVI**)	-[c]	-	-
3	SO_2Py (**1**)[d]	1.0:1.2 (**2**)	45	53
4	SO_2Tol (**5**)[d]	1.0:1.0 (**14**)	45	45
5	4-Ns (**6**)[d]	1.0:1.9 (**15**)	30	55
6	COPh (**7**)[e]	1.0:1.1 (**16**)	32	36
7	CO*p*NO_2Ph (**8**)[e]	1.0:1.2 (**17**)	25	30
8	COC_6F_5 (**9**)[e]	1.0:1.6 (**18**)	21	33
9	Boc (**10**)	-[c]	-	-
10	Fmoc (**11**)[f]	1.0:1.3 (**19**)	29	39
11	$CONMe_2$ (**12**)[g]	1.0:1.4 (**20**)	32	43

[a] Determined by ^{1}H NMR from the reaction crude; [b] Isolated yield; [c] Decomposition; [d] Reaction time 1h; [e] Reaction time 16 h; [f] Reaction time 12 h; [g] 50 ºC, 2 h.

From this study, it became apparent that none of the protecting groups seemed to have significant influence over the regioselectivity of nitration, since consistently low *ortho*/*para* ratios were observed for all the *N*-protecting groups examined, ranging from 1.0:1.0 to 1.0:1.9. However, this screening of protecting groups revealed that our catalytic system is compatible with a wide range of protected aniline derivatives. Among the groups examined, sulfonamides were highly reactive species, allowing

complete conversion to the corresponding mono-nitrated products in just 1 h of stirring at 100 ºC, regarding their electronic or coordinating properties (the aryl sulfonamide group can range in electronic properties from a *p*-tolyl group to a *p*-nitrophenyl or 2-pyridyl, entries 3-5). Amide and carbamate derivatives were also compatible with this protocol, although longer reaction times were required to achieve full conversion (12-16 hours, entries 6-8, 9-10). In these cases, the difficulty in the chromatographic separation of the *ortho*- and *para*- regioisomers (and trace amounts of the starting material), resulted in lower yields upon isolation. The *N*-Boc protected aniline **10** failed to provide the expected nitration product; instead, a complex mixture of unidentified products was formed, presumably due to the acid-lability of this protecting group (entry 9). However, the easily deprotectable *N*-Fmoc derivative **11** smoothly reacted with HNO_3 yielding a nearly equimolar mixture of *ortho*/*para* mono-nitrated products along with a small amount of decomposition products (roughly 10%). The urea **12** proved to be the most reactive substrate, enabling a decrease of the temperature from 100 ºC to 50 ºC. Under these milder reaction conditions, the corresponding nitration product was produced in good yield (75%), but again as a mixture of *ortho*/*para* regioisomers (entry 11).

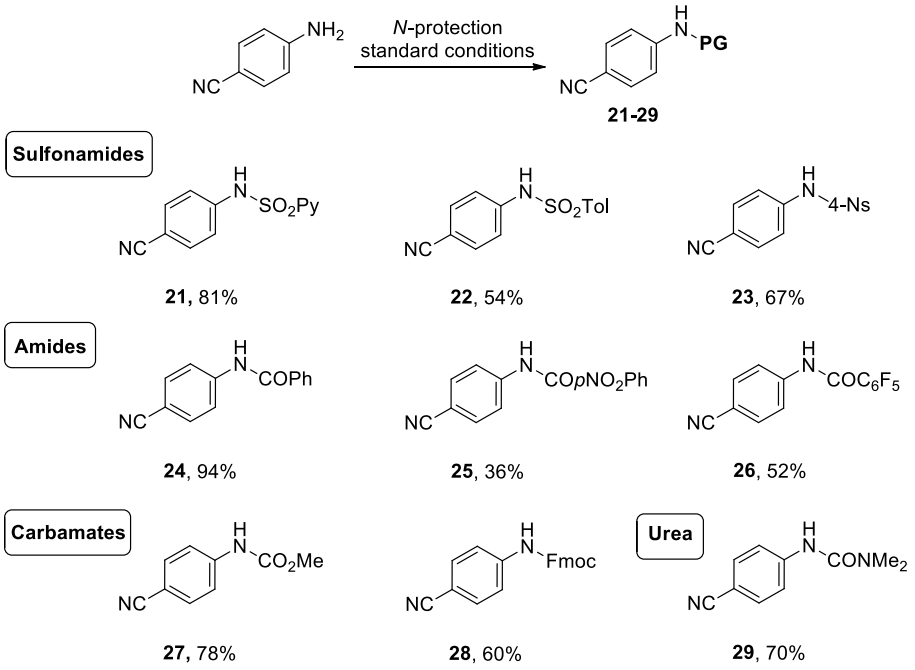
Finally, *N*-alkylation did not fit for this transformation, as demonstrated by the fact that *N*-(Me)(SO_2Py) derivative **13** was recovered unaltered, even after extended reaction times, thus highlighting the key role played by the *NH* moiety (Scheme 2.42).



Scheme 2.42

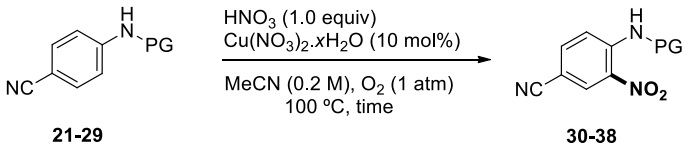
2.4.4. The reactivity profile of *para*-aminobenzonitrile derivatives

Once again, the presence of regioisomeric mixtures precluded and in-depth study of the influence of the nature of the protecting group and the reactivity profile. To address this shortcoming, we chose the 4-aminobenzonitrile core having not only the *para*-position blocked, but also presenting attenuated its reactivity towards the electrophilic aromatic substitution. This effect should allow a more easily identification of changes in the reactivity caused by small structural modifications, especially in the case of highly reactive substrates. For that purpose, 4-aminobenzonitrile was *N*-protected with the same set of protecting group previously explored in the case of aniline following standard protocols. The corresponding sulfonamides (**21-23**), amides (**24-26**), carbamates (**27** and **28**) and urea (**29**), were thus isolated in synthetically useful yields (36-94%, Scheme 2.43).

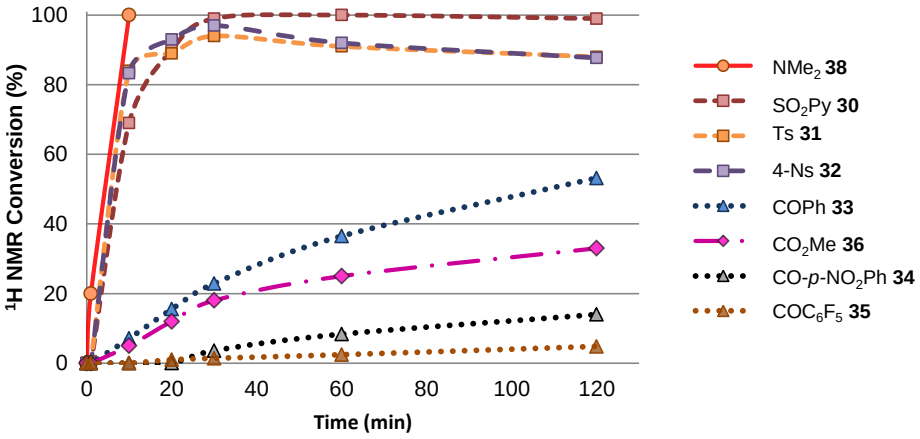


Scheme 2.43

This set of 4-aminobenzonitrile derivatives **21-29**, were next examined in the reaction with HNO_3 (1.0 equiv), under the optimized reaction conditions [$Cu(NO_3)_2{\cdot}xH_2O$ (10 mol%), O_2 (1.0 atmosphere) in acetonitrile at 100 ºC]. The reaction progress (conversion) over time, depicted in Figure 2.7, was determined in each case by integration from the ^1H NMR spectra of the crude reaction mixture. Individual experiments were set up for each point (6 time points in the range of 0-120 minutes). In order to minimize errors in the scale, a stock solution of the copper catalyst in acetonitrile was immediately prepare prior to the study. In all the cases, at given times, the reaction was quenched with a saturated solution of sodium bicarbonate in order to avoid further reaction while manipulating the sample.



21-29 **30-38**



Time (min)	SO_2Py	Ts	4-Ns	COPh	CO-*p*-NO_2Ph	COC_6F_5	CO_2Me	NMe_2
1	0	0	0	0	0	0	0	20
10	69	84	83	7	0	0	5	>98
20	90	89	93	16	0	1	12	-
30	>98	94	97	23	4	1	18	-
60	>98	91[a]	92[a]	37	8	2	25	-
120	>98	88[a]	88[a]	53	14	5	33	-

[a] The 2,6-dinitrated product is also detected as minor compound

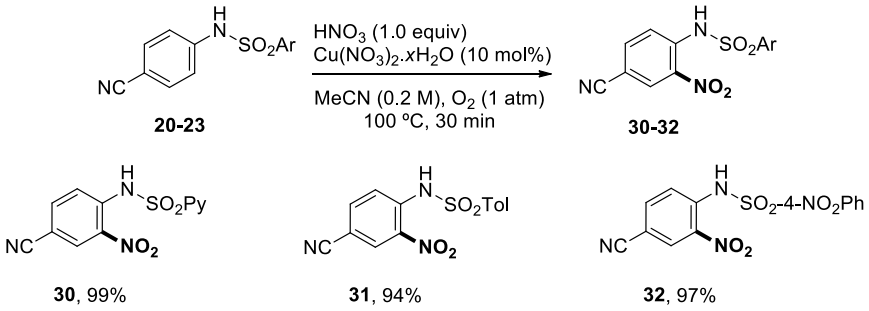
Figure 2.7. Conversion yield (%) *vs*. reaction time for the mono-nitration of 4-aminobenzonitrile derivatives 21-29

a) Sulfonamides

All the sulfonamide groups evaluated enabled a very fast nitration reaction (>90% conversion in 20 min). Among the sulfonyl groups tested, the *N*-SO_2Py **21** showed the best reactivity-selectivity balance, affording the nitroderivative **30** as the only product without detecting any di-nitration by ^{1}H NMR. This product was isolated in

99% yield. In this particular case, when the catalyst loading was reduced to 1 mol% negligible conversion was observed (<5 %), the starting material **21** was recovered unaltered. In addition to the lower reactivity of this substrate towards aromatic electrophilic substitution, this result is most plausibly ascribed to the metal-coordinating ability of the nitrile group, which could act as competitive ligand for the active intermediate, thus further decelerating the catalysis.

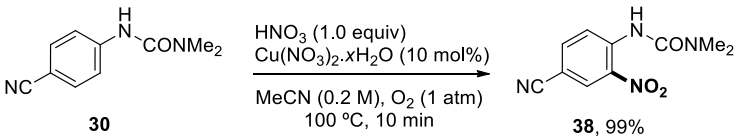
For the other two sulfonamides tested **22** [PG = Ts (4-toluensulfonyl) and **23** [PG = 4-Ns (4-nitrobenzenesulfonyl)], reaction times longer than 30 min resulted in the formation of a small amount (5-12%) of competitive di-nitration at the positions *ortho* to the amino group. Nevertheless, high yields of the corresponding nitro derivatives can be achieved if the reaction is stopped before 30 min [94 % for **31** (PG = Ts) and 97% for **32** (PG = 4-Ns)].



Scheme 2.44

b) Ureas

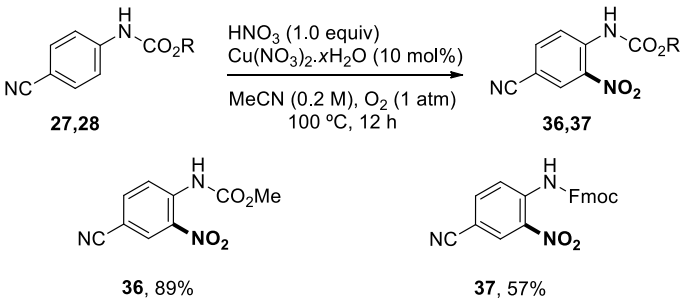
The *N*,*N*-dimethylurea **30** was even more reactive, reaching full conversion to mono-nitrated product **38** after just 10 min. The product was isolated in 99% yield by simple precipitation.



Scheme 2.45

c) Carbamates

This protocol also proved to be consonant with *N*-carbamate-protected 4-aminobenzonitrile. Although conversions below 40% were observed in the nitration of carbamate **27** after 2 h, the reaction occurred cleanly and good yield of the corresponding mono-nitrated product **36** was achieved after 12 h (89% yield). In the case of the Fmoc-protected aniline **28**, partial decomposition of the starting material prevented an accurate measure of its kinetic profile (not recorded in Figure 2.7). Despite this shortcoming, the corresponding nitro derivative **37** was obtained in a synthetically useful yield (57%) after 12 h.

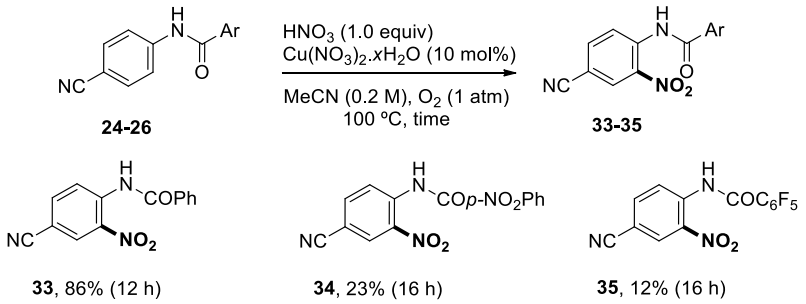


Scheme 2.46

d) Amides

The use of an aromatic amide protecting group, such as benzamide **24**, resulted also in decreased reactivity when compared to sulfonamides or ureas. In fact, the reactivity of benzamide **24** was found to be only slightly better than that of methyl

carbamate **27** (53% after 2 hours, see Figure 2.7). In accordance with the higher robustness of the amide group in comparison with carbamate, no decomposition products were detected and high yield of the *ortho*- mono-nitration product **33** was achieved after extended reaction time (86%, 12 h). The more electrophilic aromatic amides, 4-nitrobenzamide **25** and pentafluorobenzamide **26** showed a very poor reactivity (less than 15% conversion after 2 hours), even when extending the reaction times up to 16 h, upon which the corresponding nitroderivatives **34** and **35** were isolated in 23% and 12% yield respectively.



Scheme 2.47

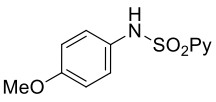
2.4.5. Structural versatility in terms of arene substitution

Once the compatibility of our catalyst system with standard nitrogen protecting groups was demonstrated, we next studied the versatility of the reaction with regard to electronic and steric modifications in the aryl ring (*para*-, *meta*- and *ortho*-substitution).

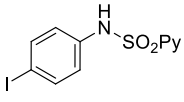
- ***Ortho*-nitration of *para*-substituted aniline derivatives**

A variety of different *para*-substituted anilines were *N*-protected following the standard protocols from the corresponding commercially available anilines. This set of aniline derivatives has been organized according to the nature of the *N*-protecting groups.

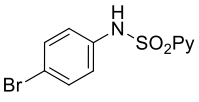
Sulfonamides



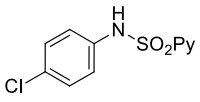
39, 90%



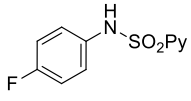
40, 89%



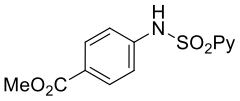
41, 87%



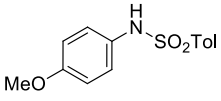
42, 76%



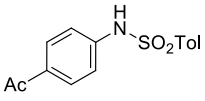
43, 79%



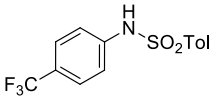
44, 64%



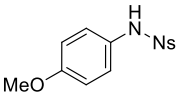
45, 84%



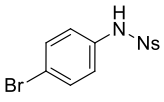
46, 75%



47, 90%

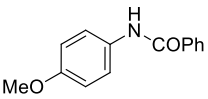


48, 77%

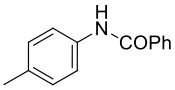


49, 82%

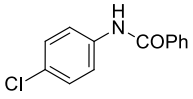
Amides



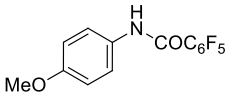
50, 94%



51, 95%

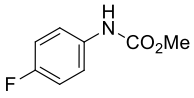


52, 91%

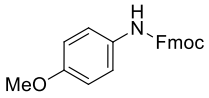


53, 79%

Carbamates



54, 84%

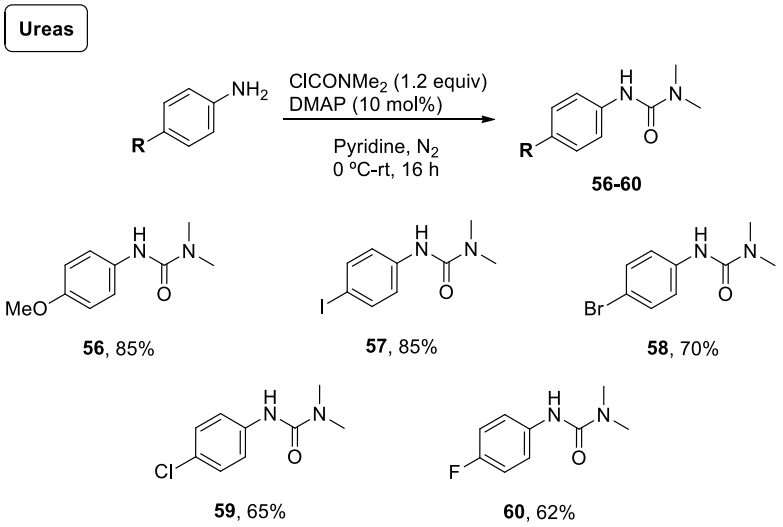


55, 73%

Scheme 2.48

Owing to the limited availability of functionalized isocyanates, substituted ureas **56-60** were prepared by following an alternative strategy based on the reaction of the corresponding functionalized aniline (1.0 equiv) with dimethylcarbamoyl chloride (1.2 equiv) using pyridine as base and solvent, and a catalytic amount of DMAP (10 mol%). Under these conditions, a variety of substituted ureas were prepared in

good yields (62-85%), most of them with an halogen as substituent, in order to explore the compatibility of this type of substitution in the Cu^{I}-catalyzed nitration reaction.



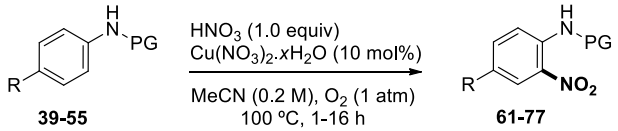
Scheme 2.49

All these *N*-protected aniline derivatives (sulfonamides, carbamates, amides and ureas) were thus submitted to the nitration reaction under the optimized reaction conditions. As shown in Schemes 2.50 and 2.51, this wide range of protected *para*-substituted anilines underwent nitration at the *ortho*-position in moderate to good yields (22 examples, 54-98% yield). Complete *ortho*-regioselectivity, with regard to the amino moiety, was observed in this set of substrates in which the *para* position was blocked, even in those cases where the blocking substituent presents a strong *ortho*-directing effect, such as the OMe group (see for instance products, **61**, **67**, **70**, **75** and **77**). Substrates bearing strong electron-withdrawing groups, such as CF_3, F, CN, CO_2Me or COMe, provided similar yields to those of substrates with electron- donating groups (OMe, Me) in terms of reaction yield.

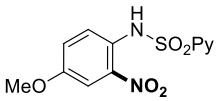
It is also important to stress the high functional-group tolerance (ester, ketone, nitro or cyano), including the halogen substitution (F, Cl, Br, I), thus, providing products suitable for further elaboration via palladium-catalyzed cross-coupling reactions. Remarkably, the survival of an iodo substituent on the aniline counterpart proved to be very challenging. In these particular case, in order to prevent deiodination by oxidative addition of Cu^{I} to the carbon–iodo bond,[124] the temperature was decreased to 50 ºC, leading to a synthetically useful 55% and 54% isolated yield of iodo derivatives **62** and **79**, respectively. It is worth to mention that in the case of Cl- or Br- substituted substrates **63**, **64**, **71**, **74**, **80** and **81** no dehalogenation products were observed, providing the desired nitro compounds in good yields (61-83%).

In accordance with our previous reactivity studies, while urea or sulfonamide derivatives reached full conversion in a short time period (from 10 min to 2 h), carbamates and amide derivatives required extended reaction times (12-16 h) to achieve high conversion and similar yields. In these cases, improved yields were obtained for those aniline bearing electron-donating groups on the aromatic ring. For example, the Fmoc protecting group, which provided a modest yield in the case of deactivated 4-aminobenzonitrile derivative (product **37**, 57% yield, Scheme 2.46), was fully tolerated for the electron-rich *p*-methoxy-substituted aniline **55**, affording the corresponding nitration product **77** in 89% yield. On the other hand, the dramatic increase in reactivity of electron-rich aniline derivatives allowed the use of the previously unreactive pentafluorobenzamide protecting group. Therefore, the *p*-methoxy derivative **53** smoothly underwent Cu-catalyzed nitration to produce the corresponding nitrocompound **75** in a moderate yield (56%). Due to the high reactivity exhibited by urea derivatives, compounds **56-60** could efficiently be nitrated at 50 ºC, just by extending the reaction time to 2 h, providing the expected nitration compounds **78-82** in moderate to excellent yields (54-94%, Scheme 2.51).

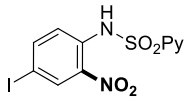
[124] For a recent review on copper-catalyzed Ullmann type chemistry, see: C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev.* **2014**, *43*, 3525 and references cited therein.



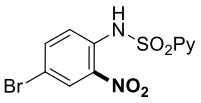
Nitration of *para*-substituted sulfonamides



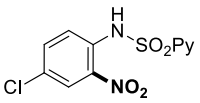
61, 98% (1 h)



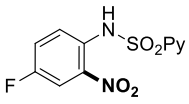
62, 55% (2 h, 50 ºC)



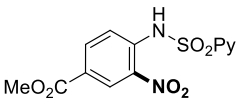
63, 77% (2 h, 80 ºC)



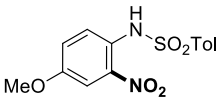
64, 89% (1 h)



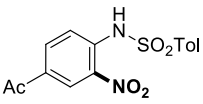
65, 83% (1 h)



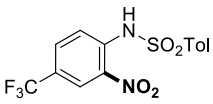
66, 80% (1 h)



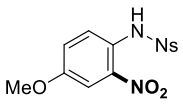
67, 90% (1 h)



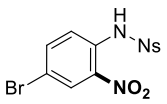
68, 77% (1 h)



69, 76% (1 h)

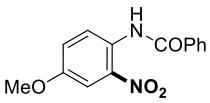


70, 90% (1 h)

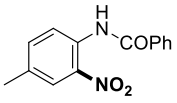


71, 76% (2 h, 50 ºC)

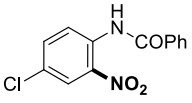
Nitration of *para*-substituted amides



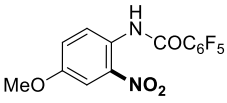
72, 85% (16 h)



73, 72% (16 h)

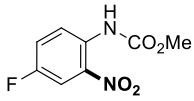


74, 83% (16 h)

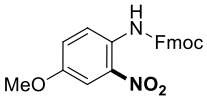


75, 56% (16 h)

Nitration of *para*-substituted carbamates

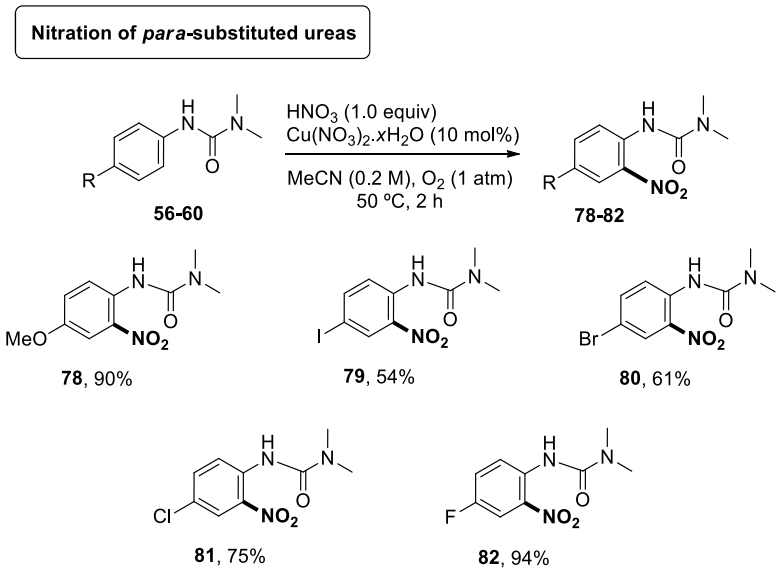


76, 90% (16 h)



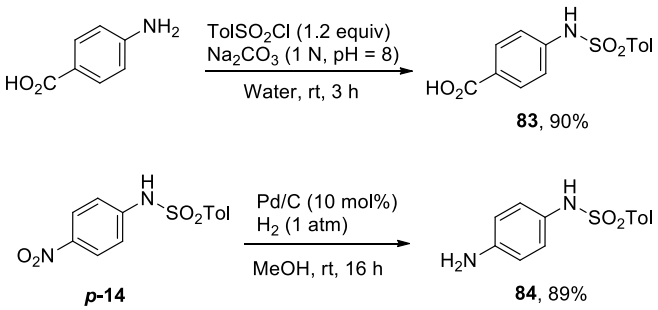
77, 89% (16 h)

Scheme 2.50



Scheme 2.51

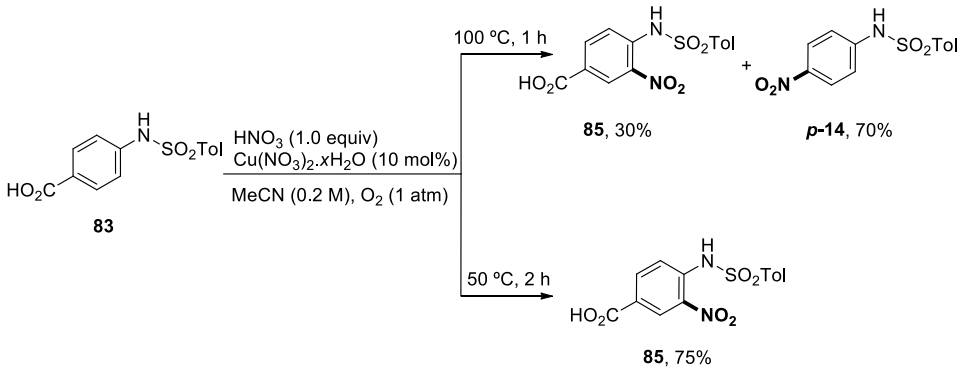
Encouraged by this excellent functional group tolerance, we were eager to test whether this nitration protocol could be compatible with more challenging aniline substrates, such as compounds **83** (bearing a free carboxylic acid moiety) and **84** (bearing an unprotected NH_2 group) (Scheme 2.52). The synthesis of the former was cleanly achieved (90% yield) from 4-aminobenzoic acid by sulfonylation in water due to the low solubility of the starting material. On the other hand, the diamino derivative **84** was prepared in very good yield (89%) from the *p*-nitro sulfonyl aniline ***p*-14** by standard reduction of the nitro functionality *via* catalytic hydrogenation.



Scheme 2.52

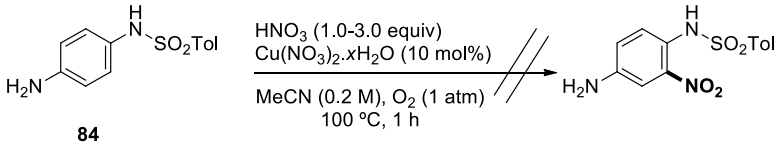
These two derivatives were next tested in the nitration protocol. When compound **83** was subjected to nitration under the above optimized conditions, the expected nitration product **85** was obtained in very low yield (30% yield), accompanied by *p*-nitro sulfonamide ***p*-14** as the main product. This result is most plausibly ascribed to a competitive nitrodecarboxylative reaction pathway leading to the *para*-nitro aniline derivative ***p*-14**.[125] To overcome this limitation, we performed the reaction at lower temperature (50 ºC) taking advantage of the high reactivity exhibited by sulfonamide derivatives in the nitration reaction. Pleasingly, under these milder reaction conditions, the desired nitration product **85** was isolated in 75% yield after 2 h, without detecting the nitrodecarboxylation product ***p*-14**, Scheme 2.53.

[125] For a nitrodecarboxylative protocol, see reference 97.



Scheme 2.53

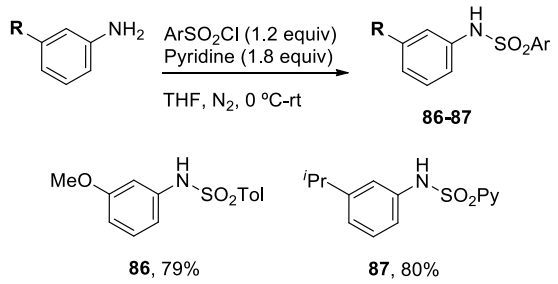
Regretfully, when *para*-amino derivative **84** was subjected to the nitration reaction a complex mixture was observed by ^{1}H NMR, probably due to the basicity of the NH_2 group, resulting in the formation of the highly deactivated ammonium salt. The addition of excess of HNO_3 (2.0 or 3.0 equiv) did not improve this outcome.



Scheme 2.54

- ***Nitration of meta-substituted aniline derivatives***

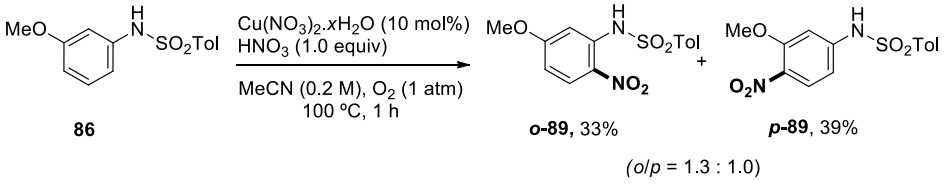
Our attention was next focused on the *meta*-substituted aniline derivatives in order to test whether the regioselectivity is controlled by steric, electronic or coordinating effects imposed by the group at the *meta*- position. To explore this issue, *N*-sulfonyl anilines **86** and **87**, which present *meta*-substituents with different steric and electronic characteristics, were easily prepared in good yields by standard *N*-sulfonylation of the corresponding commercially available anilines (79% and 80%, respectively).



Scheme 2.55

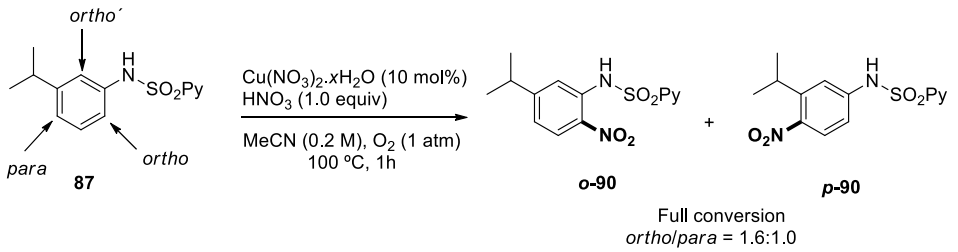
We also decided to explore the effect of a strong-electron withdrawing substituent in the *meta*- position of the aniline moiety. For that purpose, we chose the commercially available *N*-(3-cyanophenyl)benzamide **88**.

These derivatives were subsequently studied in the nitration reaction. Unfortunately, *meta*-substitution seemed not to be effective in controlling the regioselectivity since the formation of a mixture of regioisomers was observed in all the cases. To illustrate this, the nitration of *m*-methoxy-*N*-tosyl aniline **86** afforded a mixture of mono-nitrated regioisomers at C2 and C4 positions [***o*-89** (33%) and ***p*-89** (39%)] with very poor regiocontrol (*ortho*/*para* = 1.3:1.0), Scheme 2.56. The identity of both regioisomers was unambiguously established by ^{1}H NMR. The appearance of an *ortho* aryl C–H peak as a doublet with a small coupling constant in both products [7.21 ppm, *J* = 2.7 Hz for ***o*-89** and 7.14 ppm, *J* = 2.2 Hz for ***p*-89**], allowed us to exclude nitration at the most hindered *ortho* position.



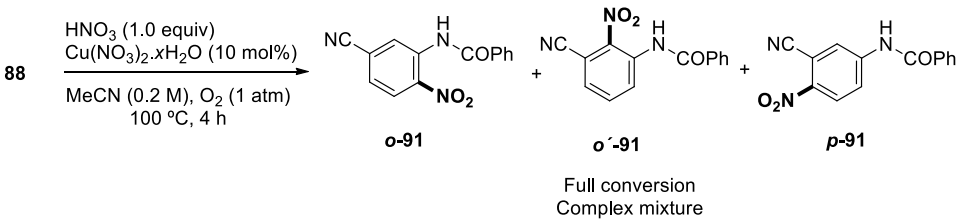
Scheme 2.56

Similarly, when aniline **87**, bearing a bulky *iso*-propyl substituent in the *meta*-position, was subjected to the nitration reaction, a 1.6:1.0 mixture of two inseparable mono-nitration regioisomers was detected by ^{1}H NMR and corroborated by GC-Mass spectroscopy. In this case, both isomers could not be separated by conventional chromatography and their identity could not be unambiguously established due to overlapping in the ^{1}H NMR signals. However they were tentatively assigned by analogy with the methoxy-substituted substrate **89**, Scheme 2.57.



Scheme 2.57

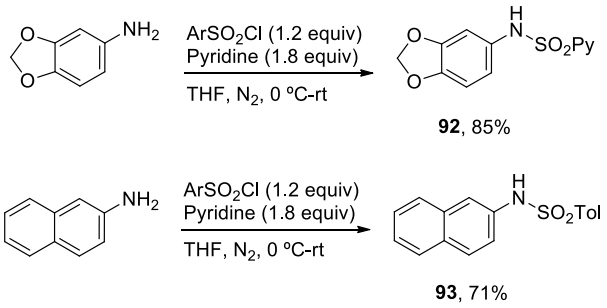
When the *meta*- position is substituted with the small cyano group (substrate **88**), a very complex, nearly equimolar mixture of *ortho*/*ortho´*/*para* diastereoisomers of three inseparable mono-nitrated products was observed by GC-Mass spectroscopy, Scheme 2.58.



Scheme 2.58

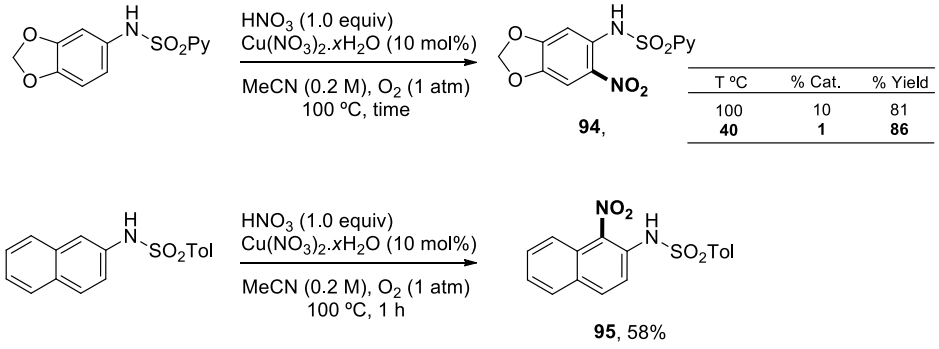
The acetal-containing aniline derivative **92** and the 2-naphthalenamine derivative **93**, having blocked both the *meta*- and the *para*-positions, were also prepared for

their evaluation as examples of polysubstituted substrates, following the standard *N*-sulfonylation protocol. The results are shown in Scheme 2.59.



Scheme 2.59

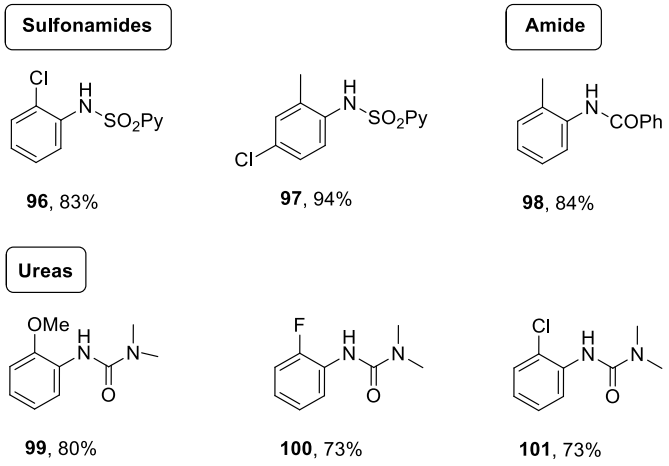
When aryl sulfonamides with 3,4-disubstitution were used as starting materials, as in the case of **92** and **93**, the corresponding nitration product was obtained as a single regioisomer. The acetal derivative **92** underwent a clean and efficient reaction at the less hindered *ortho*- position of the two available (product **94**, 81% yield). Remarkably, this highly electronically activated substrate could be nitrated at a lower temperature (40 ºC) using only 1% of catalyst loading, yielding the expected nitration product **94** (86%), proving otherwise the tolerance of this method towards the acid-sensitive acetal moiety. In the case of the 2-naphthyl derivative **93**, the reaction took place selectively at the naphtlene C-α position, *ortho* to the sulfonamido group, showing the importance of the electronic effects at the aromatic ring in the regiocontrol outcome (product **95**, 58% yield).



Scheme 2.60

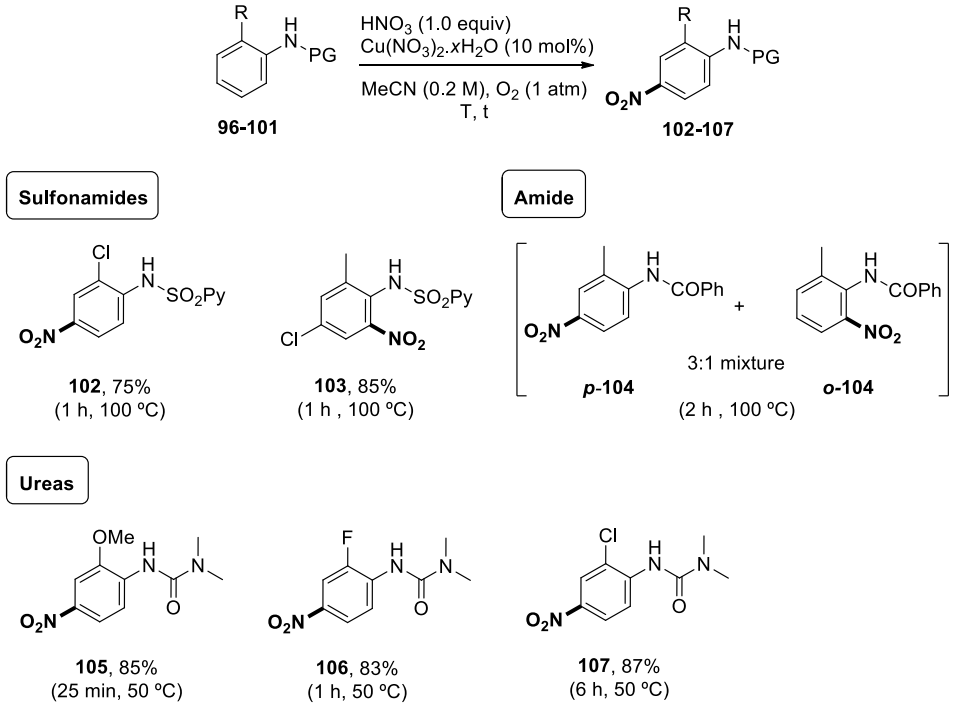
- ***Nitration of ortho-substituted aniline derivatives***

Finally, we also studied the nitration of a variety of *ortho*-substituted aniline derivatives (**96-101**). These compounds were prepared by conventional *N*-protection of commercially available derivatives.



Scheme 2.61

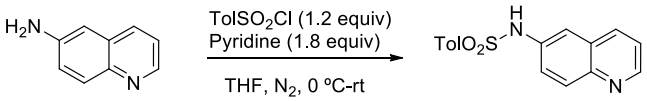
Next, the *ortho*-substituted aniline derivatives **96-101** were subjected to our nitration reaction protocol under the optimized conditions for each type of protecting group (temperature and reaction times are indicated in Scheme 2.62). Gratifyingly, most of the substrates underwent nitration at the *para*-position with complete regiocontrol and no apparent sensitivity to electronic properties of the substituent (**102**, **105-107**, 75-87% yield). The only exception to this trend was found in the nitration of the *ortho*-toluidine derivative **98**, which led to a 3:1 mixture of *para* and *ortho* regioisomers (***o*-104** + ***p*-104**). When one of the *ortho*-position and the *para*-position were blocked (substrate **97**), nitration occurred smoothly at the free *ortho*-position in good yield (**103**, 85%).



Scheme 2.62

- ***Nitration of heteroaromatic substrates***

Considering the lack of success found quite often in the direct C–H functionalization reactions of heterocyclic substrates,[126] especially those ones containing a basic nitrogen, and the fact that heteroarenes are predominant motifs in biologically active products, pharmaceuticals and organic materials,[127] we were eager to test whether this nitration protocol was compatible with heteroarenes substrates. Nevertheless, the limited number of commercially available heteroarylamines precluded the examination of a varied set of substrates. As a representative example, the quinoline derivative **108** was easily prepared by standard *N*-sulfonylation with tosyl chloride of the commercially available 6-aminoquinoline, Scheme 2.63.



108, 82%

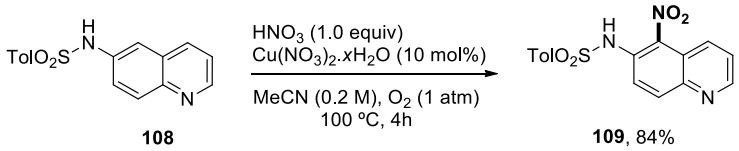
Scheme 2.63

The clean nitration of compound **108** occurred with installation of the NO_2 group at the 5-position of the heterocycle with complete regiocontrol (C-α position at the quinolone unit), to give the nitrated product **109** in 84% yield. It is remarkable that no other regioisomers were detected by ^1H NMR spectroscopy in the crude mixture. Importantly, the reaction in the absence of copper catalyst provided a complex

[126] For selected examples on C–H activation in heterocycles, see: a) D. Roy, S. Mom, S. Royer, D. Lucas, J. –C. Hierso, H. Douet, *ACS Catal.* **2012**, *2*, 1033. b) A. Dudnik, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2010**, *49*, 2096. c) I. V. Seregin, V. Ryabova, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 7742. d) N. P. Grimster, C. Gauntlett, C. R. A. Godfrey, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2005**, *44*, 3125.

[127] For a selected textbook on the application of heterocycle derivatives, see: a) A. F. Pozharskii, A. T. Soldatenkov, A. R. Katrizky, *Heterocycles in Life and Society*, WILEY, Weinheim, **2011**. For selected publications on the application of heterocycles, see: b) W. J. Pitts, *Nature* **2014**, *492*, 45. c) R. Dua, S. Shivastava, S. K. Sonwane, J. K. Srivastana, *Advances in Biological Research*, **2011**, *5*, 120.

mixture of products, confirming again the crucial role of the Cu catalysis. This result demonstrates that heteroaromatic substrates are also amenable to the reaction.



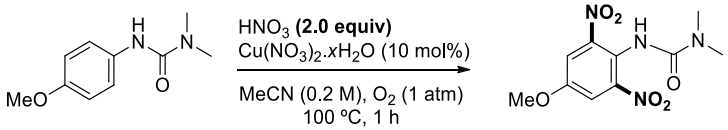
108 **109**, 84%

Scheme 2.64

2.4.6. Expanding the reaction to the dinitration of protected anilines

Capitalizing on the high reactivity of our nitration protocol, allowing the nitration of strongly deactivated aniline derivatives, we envisioned the application of this method to accessing di-nitrated anilines by using two equivalents of HNO_3. In our optimizations experiments, we observed traces of di-nitration products (identified by ^1H NMR and mass spectroscopy) when highly activated aniline derivatives were subjected to the reaction conditions. These results encouraged us to test this possibility using as the model substrate one of the most reactive ones, the *p*-OMe-substituted urea derivative **56**.

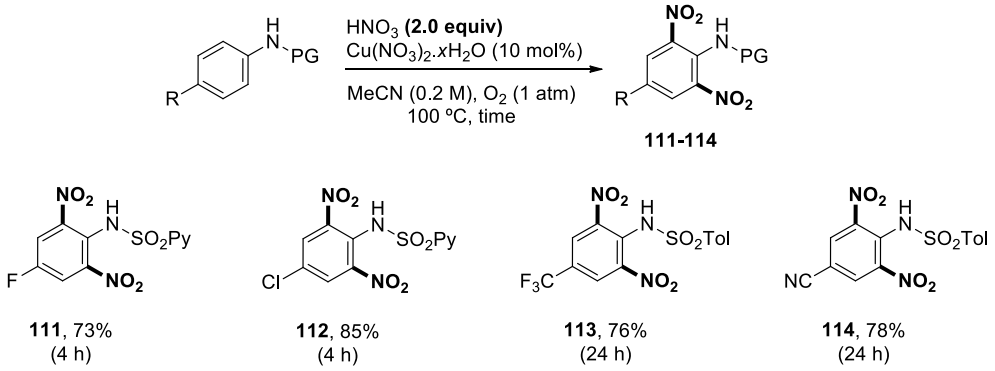
Compound **56** was then submitted to the nitration protocol using two equivalents of HNO_3 in conjunction with molecular oxygen as terminal oxidant, $Cu(NO_3)_2.xH_2O$ as catalyst, in MeCN (0.2 M) and 50 ºC for 2 h. To our delight, the desired di-*ortho*-nitroaniline derivative **110** was selectively formed in 81% yield, demonstrating that this catalytic system was also efficient for promoting a second nitration reaction.



80 **110**, 81%

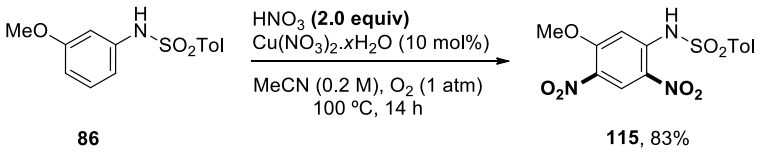
Scheme 2.65

A representative set of protected *para*-substituted anilines underwent di-*ortho* nitration in synthetically useful yields, (**111-116**, 73-85%), regardless of the electronic nature of the substituent or the identity of the protecting group at the nitrogen, showing the generality and robustness of this di-nitration transformation. Again, compatibility to halogen substitution (Cl and F, products **112**, **116** and **111** respectively) provided a useful handle for further derivatization. Even the most challenging substrates, those ones bearing a strong electron-withdrawing substituent at the aromatic ring, were well tolerated, although the catalyst loading needed to be increased to 30 mol% and the reaction time to 24 h for achieving high conversions. For example, under these slightly modified conditions, derivative **113** bearing a CF_3 and **114** holding a *para*-cyano group, were isolated in good yieldsafter 24 h (76% and 78% yield, respectively), reinforcing the robustness of this nitration method.



Scheme 2.66

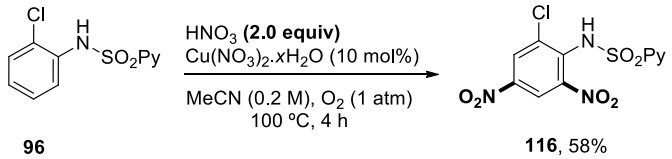
The *m*-methoxy-substituted aniline derivative **86** underwent di-nitration cleanly at the less hindered *ortho*- and the *para*-positions, affording compound **115** in 83% yield after 14 h at 100 ºC.



86 **115**, 83%

Scheme 2.67

The presence of a substituent at the *ortho*-position allowed di-nitration at both the unsubstituted *ortho*- and *para*-positions, as exemplified in the reaction of the *ortho*-chloro aniline **96**, which afforded the corresponding di-nitration product **116** in 58% yield after 4 h at 100 ºC.

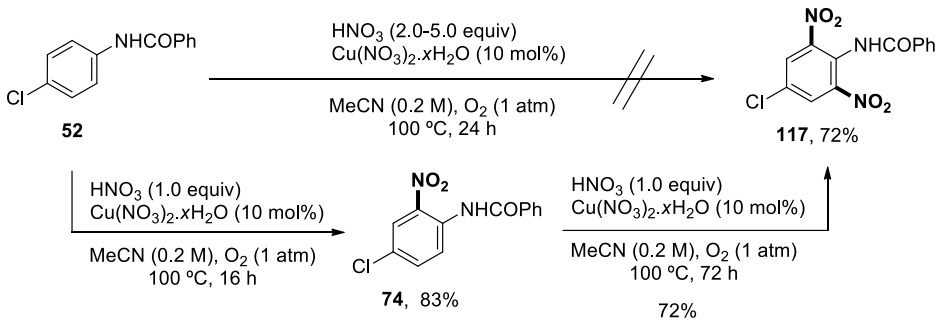


96 **116**, 58%

Scheme 2.68

Benzamides, which are less reactive compounds towards nitration, showed a different behaviour under the di-nitration reaction conditions. For instance, *para*-chloro substituted benzamide **52** did not react under the one-pot two-fold nitration to form the expected di-nitrocompound **117**, even when increasing the amount of nitric acid (up to 5.0 equiv) and the reaction time (up to 24 h). In this case, the reaction was stopped at the mono-nitration stage, affording product **74** in 83% yield.

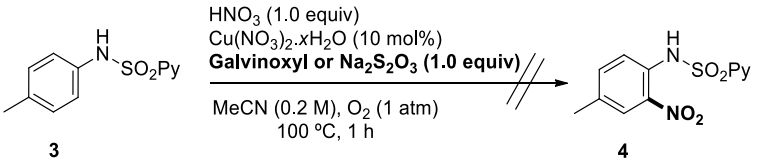
Nevertheless, the corresponding di-*ortho*-nitrobenzamide can be easily accessed in a step-wise fashion. Accordingly, submitting the pre-isolated mono-nitration derivative **74** to a second equivalent of HNO_3 under otherwise identical conditions, led to a clean formation of the di-nitro product **117** (72% yield) after prolonged reaction time (72 h).



Scheme 2.69

2.4.7. Mechanistic studies

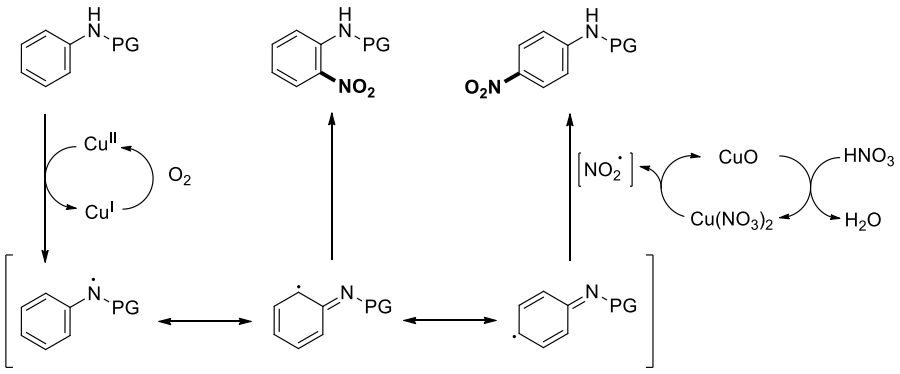
In order to gain mechanism insights for the copper-catalyzed nitration of anilines, some studies were carried out which were consistent with the hypothesis that the reaction proceeds through a radical pathway. For example, the model nitration of toluidine derivative **3** with HNO_3 was completely suppressed in the presence of radical scavengers such as *Galvinoxyl* or sodium thiosulphate, suggesting that free radical intermediate species could be involved in the reaction pathway.



Scheme 2.70

Another mechanistic consideration is the lack of reactivity of *N*-alkylated derivatives. For instance, the *N*-(Me)(SO_2Py) protected aniline **13** was found to be unreactive under the optimized conditions (see Scheme 2.42, page 110).This *N*-alkyl substitution would prevent the formation of an amidyl radical intermediate, which could be delocalized onto the aromatic ring upon one-electron oxidation by the

Cu^{II} species. This carbon-centered radical could react with $Cu(NO_3)_2$ or be intercepted by a nitrogen dioxide radical, which could be produced by thermal decomposition of $Cu(NO_3)_2$.[128] The applicability of other copper salts as precatalysts such as $Cu(OAc)_2$ and CuCl, the latter being easily oxidized to Cu^{II} under a molecular oxygen atmosphere, could be understood if anion exchange occurred with HNO_3, leading the incorporation of nitrate ions into the copper(II) moiety. A plausible mechanism is depicted in Scheme 2.71.[129]

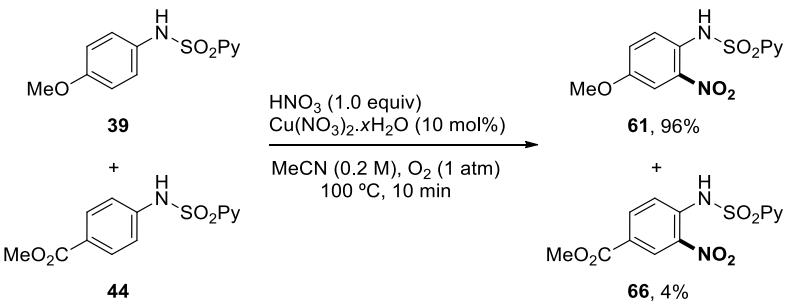


Scheme 2.71

[128] For thermal decomposition of $Cu(NO_3)_2.3H_2O$, see: a) I. V. Mozorov, K. O. Znamenkov, Y. M. Korenev, O. A. Shlykhtin, *Thermochimica Acta* **2003**, 173. The authors reported the sequential dehydration of $Cu(NO_3)_2.3H_2O$. In a first step of dehydration (40-80 ºC), $Cu(NO_3)_2.2.5H_2O$ and $Cu(NO_3)_2.H_2O$ were detected. Anhydrous $Cu(NO_3)_2$ was formed during further dehydration at 80-110 ºC. See also b) H. Wayne Richardson, *Copper Compounds in Ulmann´s Encyclopedia of Industrial Chemistry,* Wiley VCH, Weinheim, **2005**.

[129] For a related mechanism in the Cu-catalyzed *ortho* azidation of anilines, see: a) C. Tang, N. Jiao, *J. Am. Chem. Soc.* **2012**, *134*, 18924. For a review on Cu-catalyzed C–H functionalization by a single-electron transfer process, see: b) C. Zhang, C. Tanga, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464. For selected reviews on Cu-catalyzed aerobic C–H functionalization, see: c) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* **2013**, *113*, 6234. d) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062. For other recent Cu-catalyzed C–H functionalization reactions, see: e) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062. f) M. Shang, S. Z. Sun, H. X. Dai, J. –Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 3354. g) L. D, Tian, I. Popov, O. Daugulis, *J. Am. Soc. Chem* **2012**, *134*, 18237.

An intermolecular competitive reaction between electron-rich aniline **39** and electron-deficient aniline **44**, was conducted in order to gain further mechanistic insights. In a one-pot experiment, 1.0 equiv of aniline **39** (*p*-OMe) and 1.0 equiv of aniline **44** (*p*-CO_2Me) were subjected to the optimized reaction conditions, with 1.0 equiv of HNO_3, $Cu(NO_3)_2$ (10 mol%) and molecular oxygen as terminal oxidant. The reaction was stopped with aqueous solution of saturated $NaHCO_3$ at low conversion (after 10 min). Analysis of the crude reaction mixture by ^{1}H NMR revealed a great preference for the electronically rich aniline **39** over the electron-deficient **44** (product ratio **61**/**66** = 96:4), Scheme 2.72. This result is consistent with the proposed radical mechanism pathway, as the electrophilic $NO_2^{\bullet}$ radical usually displays a marked preference for electron-rich substrates, as seen here. Consequently, the reaction rate is expected to be faster for those aniline derivatives bearing activating substituents, while electron-demanding substituents present a slower reaction rate. This electronic preference is consistent with literature nitration precedents.[52]

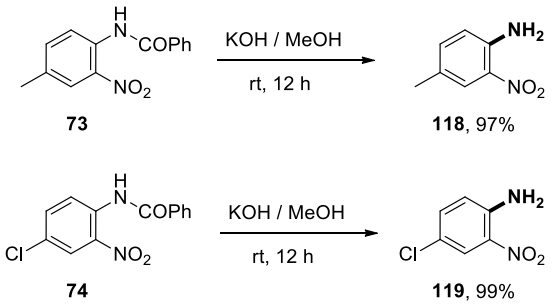


Scheme 2.72

2.4.8. Deprotection and synthetic applications

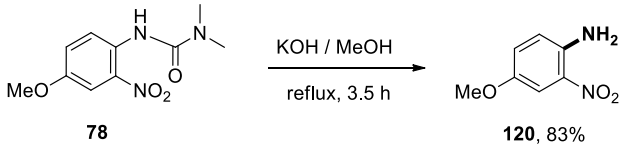
Taking advance of the flexibility of this methodology with regard to the nature of the aniline protecting group, different possibilities for the amino deprotection without affecting the nitro-group functionality can be devised as illustrated in Schemes 2.73-2.75. For example, *ortho*-nitro benzamides **73** and **74** were hydrolyzed in a methanolic solution of KOH (at rt for 12 h) yielding the corresponding functionalized

nitroaniline derivatives **118** and **119** in almost quantitative yield (97-99%), Scheme 2.73.



Scheme 2.73

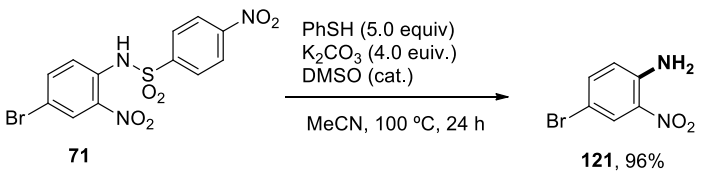
Similarly, the nitro urea derivative **78** was also deprotected under basic conditions without affecting the nitro group. However, in accordance with the greater robustness of ureas than amides as protecting group, harsher reaction conditions were required (refluxing the reaction mixture over 3.5 h). Nevertheless, deprotected nitroaniline **120** was isolated in 83% yield after sequential acid/base work up.



Scheme 2.74

Anilines protected with a nosyl group (*p*-nitrophenylsulfonyl) can be easily deprotected under mild conditions by reaction of a soft nucleophilic agent in the presence of a base, such as $PhSH/K_2CO_3$. This reaction involves the nucleophilic addition of a thiolate to the deactivated aromatic ring forming a Meizenheimer complex, which after SO_2 extrusion liberates the corresponding free amine. As an

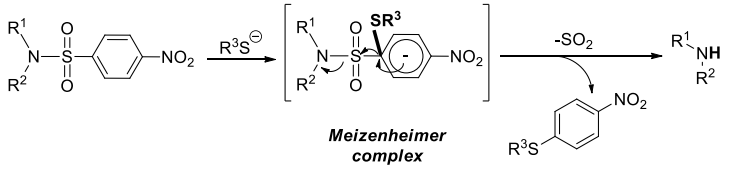
example, compound **121** was obtained in 96% yield from the *N*-nosyl nitroaniline **71** following this deprotection protocol.[130]

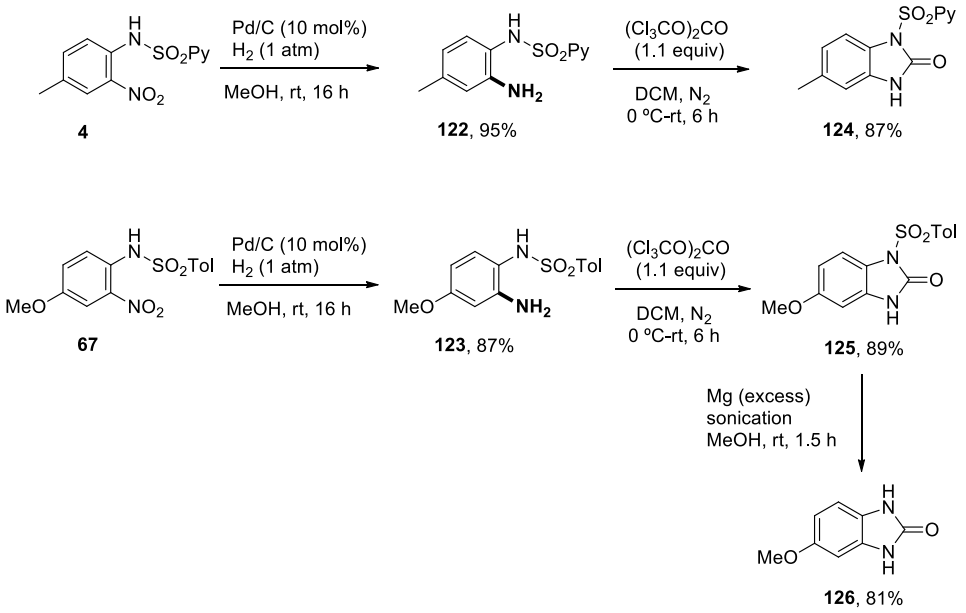


Scheme 2.75

On the other hand, nitroaniline derivatives can be considered as orthogonally protected 1,2-diaminobenzenes which are very valuable and chemically versatile building blocks towards the construction of more complex heterocyclic ring systems. Either of the two masked amino groups can easily be converted into the free NH_2 in a selective fashion. Thus, catalytic hydrogenation[42] (Pd/C, H_2) of the amino group of **4** and **67**, furnished the corresponding diamino benzene derivatives **122** and **123** in high yields (95% and 87%, respectively). These products can be further derivatized into the corresponding 1*H*-benzo[*d*]imidazole-2(3*H*)-ones **124** and **125** by using 1.1 equiv of triphosgene in DCM (87% and 89% yield, respectively). Easily deprotection of the *N*-tosyl group was demonstrated by treating **125** with Mg turnings at room temperature under sonication, afforded the *NH* free imizadolone **126** in 81% yield, Scheme 2.76.

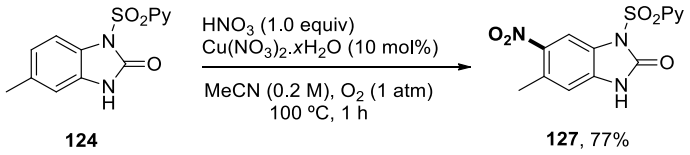
[130] For the proposed deprotection mechanism, see Scheme bellow: T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353.





Scheme 2.76

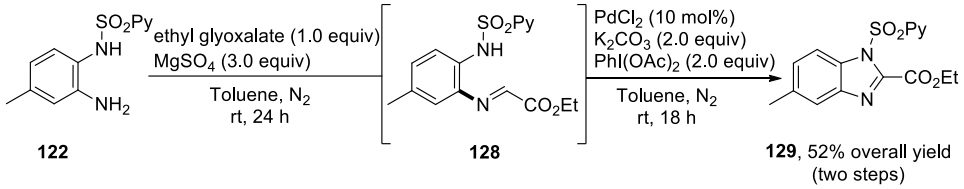
Interestingly, the heterocyclic compound **124** is well-suited for a subsequent nitration reaction under the copper-catalyzed methodology. This nitration selectively occurred at the *para*-position with regard to the free *NH* group, which is in accordance with the proposed radical mechanism. The corresponding nitro derivative **127** was obtained in 77% yield (100 ºC, 1 h).



Scheme 2.77

Finally, we further demonstrated the versatility of the orthogonally protected *o*-aminoaniline derivatives for the construction of heterocyclic architectures. The

palladium-catalyzed cyclization through the cascade sulfonamidation-oxidation of glyoxalate-derived imine **128**, obtained *in situ* from condensation of aniline **122** with ethyl glyoxalate, led to the formation of the benzimidazole derivative **129** in a reasonable 52% overall yield.

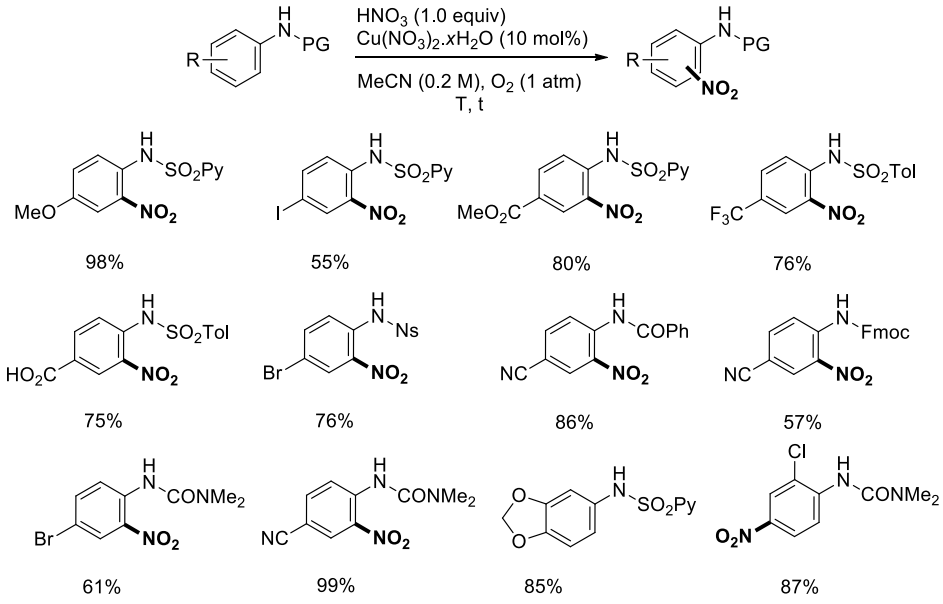


Scheme 2.78

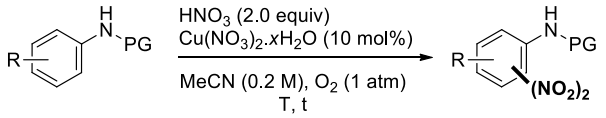
2.5. Conclusions

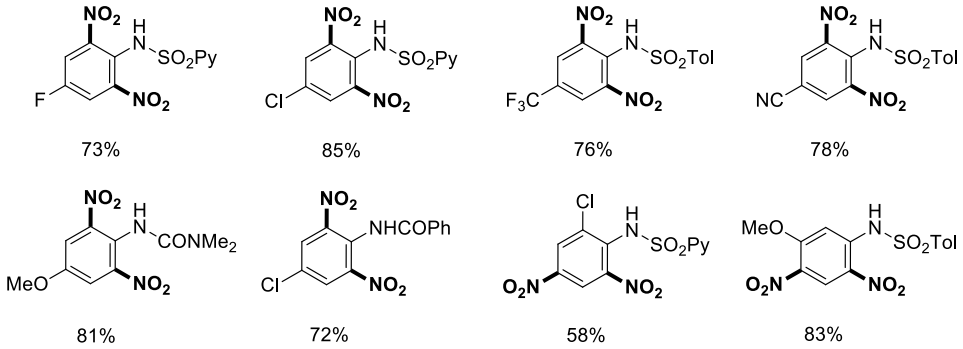
1) We have developed a reliable, amenable to scale-up, Cu-catalyzed procedure for the selective nitration of *para*-substituted and *ortho*-substituted aniline derivatives by using one equivalent of HNO_3 and molecular dioxygen as terminal oxidant which produces water as the only stoichiometric by-product. The use of inexpensive, safe and easy to handle copper salts and the possibility of employing MeCN or mixtures of MeCN/H_2O as solvent, also contributed to the eco-friendliness character of our protocol.

2) This system is compatible with a wide range of *N*-protecting groups and features remarkable tolerance with regard to arene substitution, including highly electron-deficient groups (CN, CO_2H, CF_3, CO_2Me), and acid sensitive groups (acetal). The high reactivity displayed by some derivatives, especially ureas and sulfonamides, enable the survival of halogen substituents, including Br and, especially, I, which is a distinct feature of a Cu-catalyzed protocol. In addition, the regioselectivity of the nitration is highly predictable depending on the substitution pattern of the substrate.

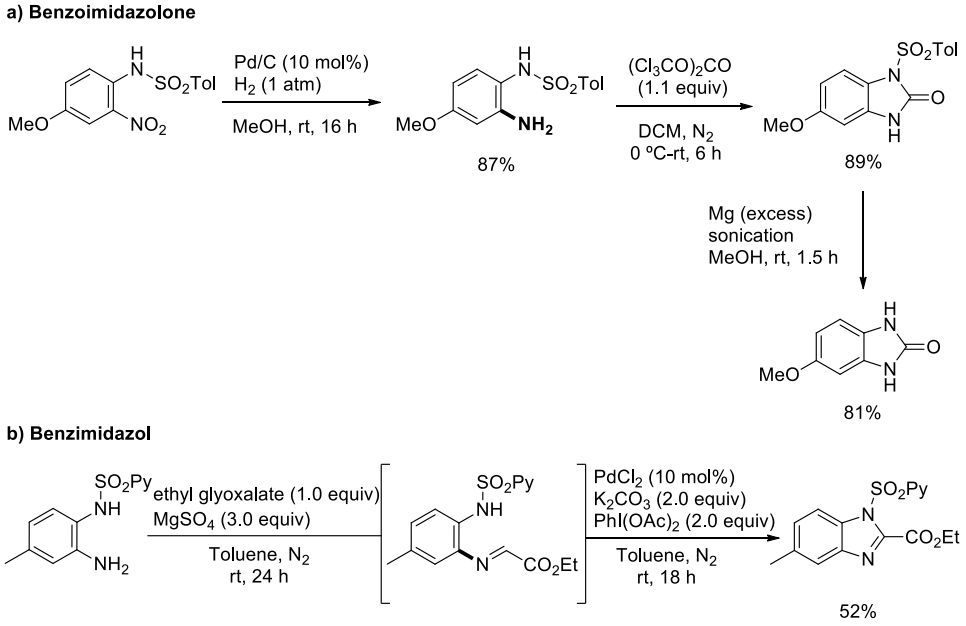


3) This methodology is also efficient for the two-fold nitration by just using two equivalents of HNO_3 (instead of one) under otherwise identical reaction conditions. A variety of di-nitrated aniline derivatives can be accessed through this protocol.





4) Both the NO_2 and the NH functionalities, which can be considered as two orthogonally protected amino groups, provide products that offer high versatility as building blocks for the synthesis of heterocyclic scaffolds. As two applications of the synthetic potential of this method, the efficient assembly of 1*H*-benzo[*d*]imidazole-2(3*H)*-ones and benzimidazole derivatives, have been emphasized.

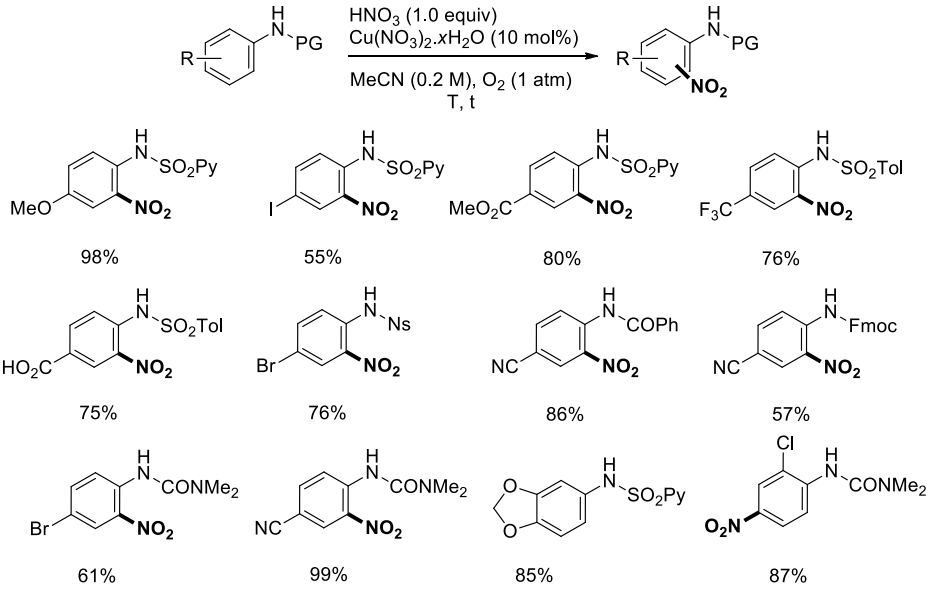


5) Although a detailed mechanism of this Cu^{II}-catalyzed nitration protocol remains to be elucidated, preliminary insights suggest a SET pathway with participation of highly electrophilic $NO_2^{\bullet}$ radicals. For example, the reaction was completely inhibited in the presence of radical scavengers such as *Galvinoxyl* and sodium thiosulphate. In addition, a marked preference for electron-rich substrates over electron-poor was observed in intermolecular competition experiments.

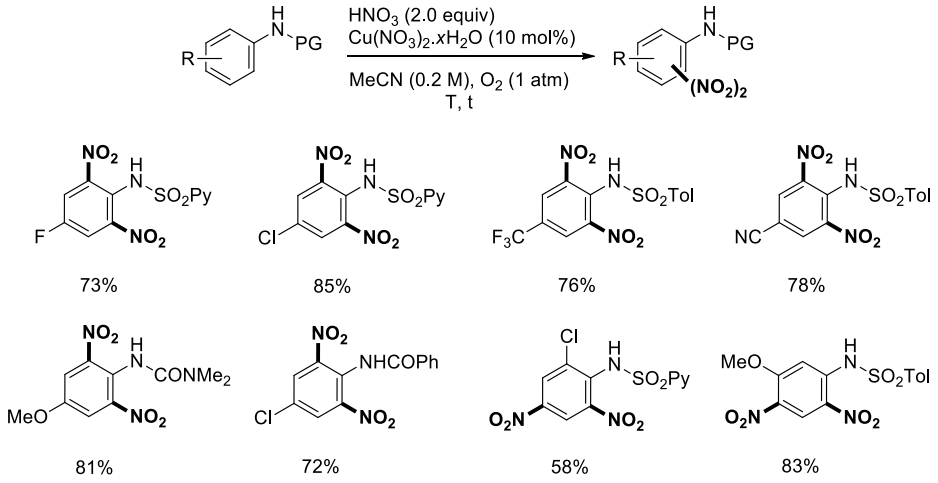
2.9. Conclusiones

1) Se ha desarrollado un método de nitración altamente selectivo, eficaz y escalable, catalizado por Cu, para la nitración de anilinas *para*- y *orto*-sustituidas, utilizando HNO_3 como fuente de grupos nitro y oxígeno molecular como oxidante terminal, generando únicamente H_2O como subproducto estequiométrico. El uso de sales de cobre, las cuales son baratas y fácilmente manejables, y la utilización de MeCN o mezclas de MeCN/H_2O como disolvente, contribuyen en aumentar el carácter respetuoso con el medio ambiente de nuestro método.

2) Este sistema de nitración resulta ser compatible con un gran número de grupos protectores de aminas y exhibe una gran tolerancia en los patrones de sustitución del anillo aromático de la anilina, incluyendo grupos altamente deficientes de electrones tales como CN, CO_2H, CF_3, CO_2Me y grupos sensibles a medios ácidos como por ejemplo el grupo acetal. La alta reactividad observada para algunos derivados, especialmente en el caso de las ureas y las sulfonamidas, permitió llevar a cabo la reacción de nitración en presencia de halógenos. Cabe destacar la tolerancia al Br y especialmente al I, lo cual otorga un valor añadido a nuestro método catalizado por cobre. Además, los diferentes patrones de sustitución en el anillo aromático, *orto*,*meta* o *para*, permiten predecir la regioselectividad de la reacción.

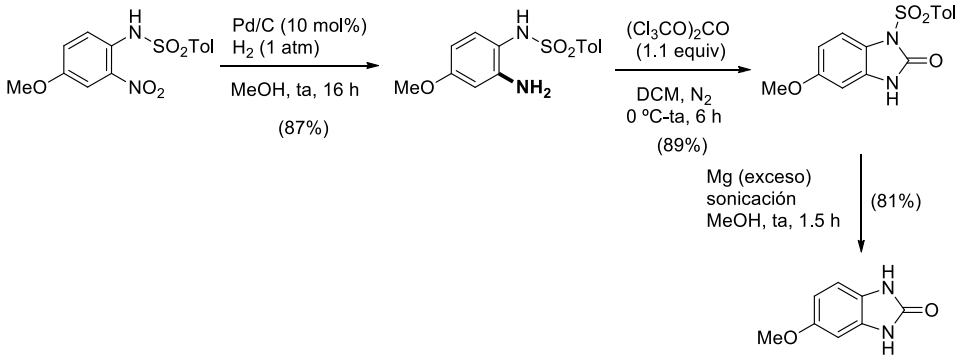


3) Mediante un ajuste de las condiciones de reacción, aumentando la cantidad de HNO_3, de 1.0 a 2.0 equiv, se pudo llevar a cabo la reacción de di-nitración en una gran variedad de anilinas.

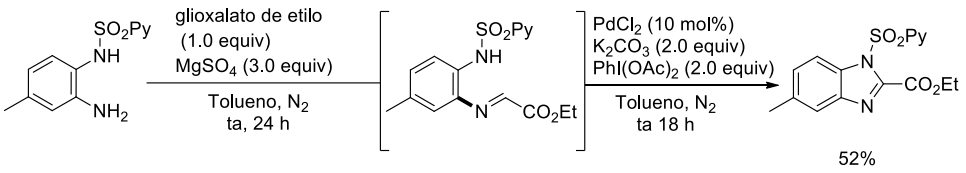


4) Los grupos NO_2 y N*H*-PG pueden ser considerados como dos grupos aminos ortogonalmente protegidos, los cuales pueden ser desprotegidos selectivamente dando acceso a unidades sintéticas precursoras de heterociclos complejos. Por ejemplo, la aplicabilidad sintética del método fue demostrada mediante la síntesis de derivados de benzimidazol.

a) Benzoimidazolona



b) Benzimidazol



5) Aunque no se ha profundizado en el mecanismo detallado de este proceso catalizado por Cu, estudios preliminares sugieren un proceso de transferencia electrónica. Por ejemplo, la presencia de inhibidores radicálicos, tales como el *Galvinoxyl* o el tiosulfato de sodio, inhibieron completamete la reacción de nitración. Por otro lado, el estudio competitivo de una anilina rica en electrones frente a otra pobre en electrones, demostró que la nitración de la primera es un proceso mucho más rápido.

Chapter 3:

Palladium-catalyzed γ-C(sp^3)–H carbonylation of amino acid derivatives

3. Palladium catalyzed γ-C(sp^3)–H carbonylation of amino acid derivatives

3.1. Relevance of amino acid and peptide derivatives

In recent years, the pharmaceutical industry has experienced a paradigm shift from small molecules, which had long been thought of as the ultimate drugs, to peptide-based therapies because peptides offer lower toxicity, show higher specificity and demonstrate fewer toxicology issues compared to small molecule drugs.[131]

In this context, although natural peptides and proteins are of great importance in present day drugs discovery programs, modification of these therapeutics with non-natural amino acids of desired structural complexity is instrumental to identify target-specific peptides and/or to improve pharmacokinetic properties when compared to their natural counterparts.[132]

Amino acids are not only subunits of peptides and proteins, but also they are essential building blocks in total synthesis and ligand elaboration for chiral catalysis.[133] Because of their broad spectrum of applications and limited number of amino acids genetically encoded, there is an urgent need for the development of new

[131] a) A. A. Kaspar, J. M. Reichert, *Drug Discovery Today* **2013**, *18*, 807. b) D. J. Craik, D. P. Fairlie, S. Liras, D. Price, *Chem. Biol. Drug Des.* **2013**, *81*, 136. c) F. Alberico, H. G. Kruger, *Future Med. Chem.* **2012**, *4*, 1527. d) P. G. Vasudev, S. Chatterjee, N. Shamala, P. Balaram, *Chem. Rev.* **2011**, *111*, 657. e) C. Katz, L. Levy-Beladev, S. Rotem-Bamberger, T. Rito, S. G. D. Rüdiger, A. Friedler, *Chem. Soc. Rev.* **2011**, *40*, 2131. f) P. Kast, *ChemBioChem.* **2011**, *12*, 2395. g) S. Sommer, N. D. Weikart, A. Brockmeyer, P. Janning, H. D. Mootz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9888.

[132] For comprenhensive reviews on peptidomimetics, see: a) A. Grauer, B. König, *Eur. J. Org. Chem.* **2009**, *30*, 5099. See also: b) T. S. Young, P. G. Schultz, *J. Biol. Chem*. **2010**, *285*, 11039. c) J. J. Nestor, *Curr. Med. Chem.* **2009**, *16*, 4399.

[133] For a selected textbook on the use of amino acids as important building blocks, see: a) G. M. Coppola, H. F. Schuster, *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*, Wiley, New York, **1987**. See also: b) C. C. Liu, P. G. Schultz, *Annu. Rev. Biochem.* **2010**, *79*, 413.

methodologies for the straightforward chemical modifications of amino acids and peptides.[134]

3.2. Relevance and challenges of C–H bond functionalization

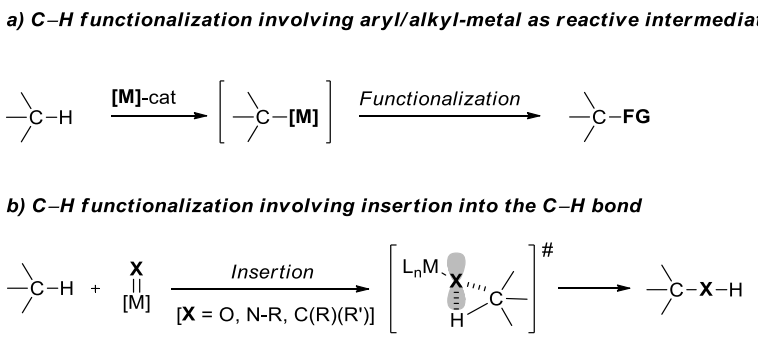
As mentioned in the introduction of this Thesis, the development of catalytic methodologies that allow conversion of inert C–H bonds into various functional groups has undergone an explosive growth in recent years. However, the direct functionalization of unactivated C–H bonds still remains a tremendous challenge owing to a confluence of factors that render them inert under most reaction conditions: (1) The two atoms are held together by a strong covalent bond with a dissociation energy in the range 90-100 kcal/mol; (2) The bond acidity is low, generally the pK_a values lie between 45 and 60, meaning that heterolytically cleavage of an unactivated C–H bond by treatment with a strong base is generally not a viable approach; (3) Due to their "paraffin" nature, they have high-lying lowest unoccupied molecular orbitals (LUMO) σ* and low-lying highest occupied molecular orbitals (HOMO) σ; (4) Over-oxidation of functionalized products is often highly thermodynamically favoured; (5) Most organic molecules contain many different C–H bonds and achieving selective reactivity of the desired bond is often very challenging.

In light of the above-mentioned challenges, transition metal-catalysis has emerged as a powerful tool for cleaving inert C–H bonds. In this field, two fundamentally different approaches for C–H functionalization have been established (Scheme 3.1).[135] The most traditional "C–H activation" approach, often termed

[134] For a selected texbook on the synthesis of amino acids, see: a) M. A: Blaskovich, *Handbook of Syntheses of Amino Acids: General Routes for the Syntheses of Amino Acids*, Oxford University Press, New York, **2010**. For a selected review on the synthesis of amino acid derivatives *via* cross-coupling reactions, see: b) D. Ma, Q. Cai, *Acc. Chem. Reseach*, **2008**, *41*, 1450.

[135] Free radicals are also capable of abstracting the hydrogen atom of an unreactive C–H bond to form a new, highly reactive C$^{\bullet}$ species, which can readily be functionalized. For selected examples, see: a) F. O´Hara, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2013**, *135*, 12122. b) W. R. Bowman, J. M. D. Storey, *Chem. Soc. Rev.* **2007**, *36*, 1803. c) D. C. Harrowven, B. J. Sutton, S. Coulton, *Org. Biomol. Chem.* **2003**, *1*, 4047. Additionally, it has long been established that enzymatic

"catalytic C–H functionalization", proceeds through a mechanistic proposal that involves the direct generation of carbometallated C–[M] (M = transition metal) intermediates, generally *via* insertion of the metal into the C–H bond, followed by a subsequent reaction with a suitable nucleophile or electrophile, to introduce the organic substituent [Scheme 3.1a, (functional group = FG)]. This "inner sphere" mechanism has proved to be an effective strategy with a broad range of substrates and reagents. An alternative type of "outer sphere" mechanism proceeds *via* the direct interaction of the C–H bond being functionalized with a ligand coordinated to the transition metal (Scheme 3.1b). This mechanism has widely been exploited both in metal-catalyzed carbene/nitrene insertions into C–H bonds and in metal-oxo-catalyzed C–H bond cleavage.[136]



Scheme 3.1

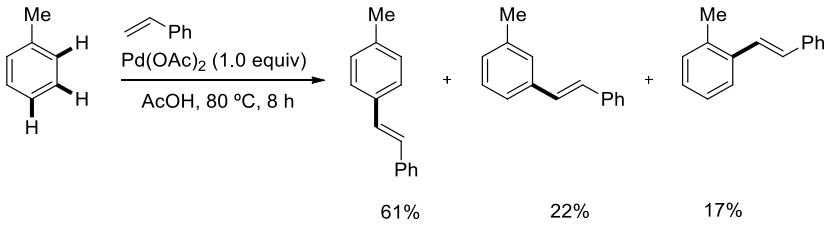
systems, such as Cytochrome P450 are capable of oxidizing unactivated C–H bonds. For a selected textbook, see: P. R. Ortiz de Montellano, *Cytochrome P450*, *Structure, Mechanism and Biochemistry*, Kluwer Academics, New York, **2005**. For selected reviews on the cross-dehydrogenative coupling of C(sp^3)–H bonds, see: d) S. A. Girad, T. Knauber, C. –J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74. e) W. J. Woo, C. J. Li. *Top. Curr. Chem.* **2010**, *292*, 281.

[136] For selected reviews on catalytic C(sp^3)–H functionalization by metal carbenoid and nitrenoid insertion, see: a) H. M. L. Davies, D. Morton, *Chem. Soc. Rev*. **2011**, *40*, 1857. b) H. M. L. Davies, J. R. Manning, *Nature*, **2008**, *451*, 417. c) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861.

Since the research of this Thesis relies on the former mode of reactivity, the discussion hereafter is focussed on the precedents on that area. The latter approach is outside the scope of this chapter and will thus not be discussed. Even so, this is a very large, diverse and highly active field. As a consequence, the aim of this introduction section is not to provide a comprehensive sampling of the vast literature. Rather, our goal in the next section is to convey some general background and insight to help the reader to put into context the research of this chapter. Subsequently, we will discuss in more detail literature precedents related to the Pd-catalyzed activation of "inert" C(sp^3)–H bonds with a special focus in the synthesis of amino acids.

3.3. Use of directing groups for achieving site-selectivity in C–H functionalization

The C–H activation protocol with $Pd(OAc)_2$ disclosed by Fujiwara and Moritani in 1968,[137] in which an arene such as benzene or toluene (used as solvent) was added to styrene to afford diarylethylenes, pointed out one of the major challenges of this new chemistry: the control of site-selectivity when multiple C–H bonds are present in the substrates. In fact, when monosubstituted benzene derivatives, such as toluene or anisole were subjected to the olefination reaction, undesired mixtures of regioisomeric products were generally formed (Scheme 3.2).[138]

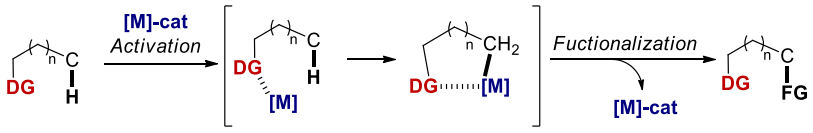


Scheme 3.2

[137] a) Y. Fujiwara, I. Moritani, M. Matsuda, S. Teranishi, *Tetrahedron Lett.* **1968**, *9*, 3863; b) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166.

[138] Y. Fujiwara, I. Moritani, R. Asano, *Tetrahedron* **1969**, *25*, 4815.

In response to this problem, the development of *ligand-directed C–H activation* has proved to be essential to address the challenges of improving reactivity and controlling regioselectivity.[139] This strategy involves the use of substrates bearing a coordinating functional group (**DG** in Scheme 3.3) that can reversibly chelate to the transition metal and brings it in close proximity to the unactivated C–H bond, thereby facilitating its cleavage (activation). The resulting cyclometallated complex, formed upon C–H cleavage, could then react with proper reagents to afford functionalized products. The energy being released from the formation of stable (generally five-membered) metallacyclic systems *via* coordination of a heteroatom to the metal center is believed to be responsible for the observed high efficiency and selectivity.[140]



Scheme 3.3

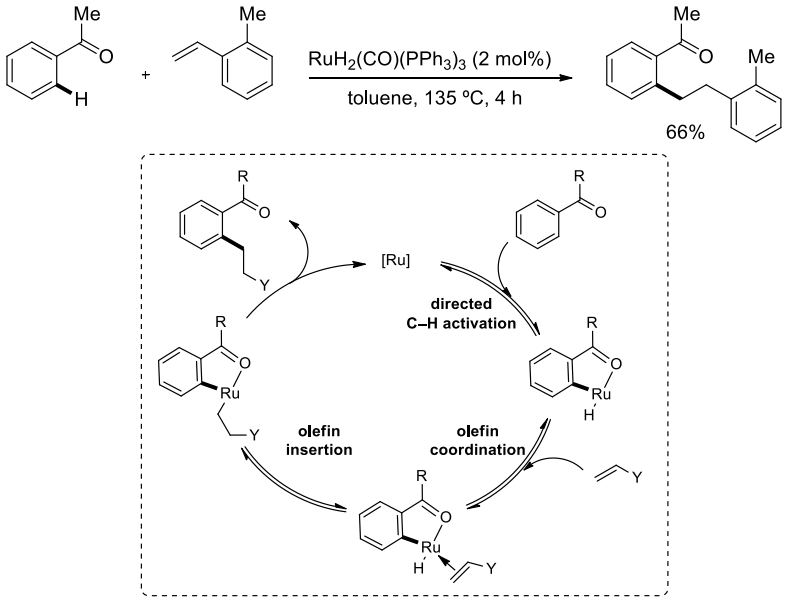
Although the first report of ligand-directed C–H *ortho*-metallation appeared in 1965 using azobenzene and stoichiometric amounts of Ni by Cope and Siekman,[141] it was not until 1993 when Murai and co-workers reported the pioneering catalytic directed C–H functionalization of aromatic ketones with olefins catalyzed by

[139] For selected recent reviews on controlling regioselectivity in C–H bond functionalization, see: a) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front*. **2015**, DOI: 10.1039/C5QO00004A. b) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res*. **2012**, *45*, 936. For recent reviews on the use of removable directing groups in metal catalysis, see: c) C. Wang, Y. Huang, *Synlett.* **2013**, *24*, 145. d) G. Rousseau, B. Breit, *Angew. Chem, Int. Ed*. **2011**, *50*, 2450.

[140] Another mode of substrate-controlled regioselectivity involves the activation of C–H bonds in substrates containing halogen substituents. The transition metal catalysts are brought adjacent to the C–H bond of interest for selective cleavage *via* oxidative addition of the carbon-halogen (C–X) bond, thereby generating organometallic intermediates as the requisite active catalysts prior to C–H activation. For a selected review, see: a) M. Catellani, E. Motti, N. Della Ca, *Acc. Chem. Res.* **2008**, *41*, 1512.

[141] A. C. Cope, R. W. Siekman, *J. Am. Chem. Soc.* **1965**, *87*, 3272.

ruthenium complexes.[142] As shown in Scheme 3.4, the reaction mechanism proposed by the authors involved the chelation-directed C–H bond activation by the ketone group to form the cyclometallated ruthenium hydride complex, followed by olefin insertion and reductive elimination to yield the expected product.



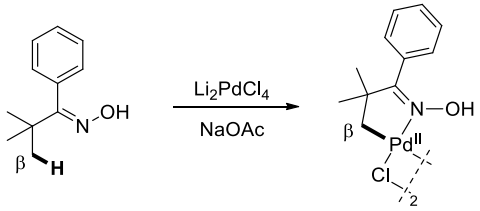
Scheme 3.4

In the context of C(sp^3)–H activation, the pioneering work of McDonald, Shaw and co-workers in 1978,[143] served as a conceptual prerequisite for a series of recently developed Pd^{II}-catalyzed C(sp^3)–H functionalization reactions. Under stoichiometric palladium (Li_2PdCl_4) and in the presence of NaOAc as base, the authors isolated a dimeric palladium(II) complex where the C–H activation process

[142] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529.

[143] A. G. Constable, W. S. McDonald, L. C. Sawkins, B. L. Shaw, *J. Chem. Soc. Chem. Commun.* **1978**, 1061.

occurred at one of the methyl groups of the oxime derivative (β-carbon), thus demonstrating the feasibility of directed inert C(sp^3)–H bond activation (Scheme 3.5).



Scheme 3.5

Since these initial reports, many research groups have expanded the scope of this strategy to include a wide variety of directing groups, which can be classified conventionally as belonging to one of two principal classes: removable or non-removable (auxiliary). These methods are commonly referred to as "directed C–H bond functionalization". Some of these directing groups, such as pyridine, may be very difficult to remove and unfortunately not desired in the final target, which limits the application of this strategy in the synthesis of complex molecules. Especially interesting from a synthetic practicality standpoint are temporary auxiliary directing groups that can easily be removed (or transformed into other desirable functional groups) after the C–H functionalization event and, consequently, are receiving growing interest in both C(sp^2)–H and C(sp^3)–H functionalization processes.[139c]

3.4. Pd-catalyzed activation of inert C(sp^3)–H bonds: late stage functionalization of amino acid derivatives

The vast majority of direct C–H bond functionalization reactions studied to the date involve the cleavage of aromatic C(sp^2)–H bonds at the *ortho* position to the directing group. The ease of activating this type of bond can be attributed to the stabilizing interaction of the arene π-system with the transition metal and by the formation of a strong aryl-metal bond. This strategy has provided chemists with a

variety of new tools, involving the formation of C–C and C–X bonds, for the efficient and reliable transformation of (hetero)arene systems.[144]

Allylic,[145] benzylic[146] or C(sp^3)–H bonds in the α-position to an electron-withdrawing group or a heteroatom[147] also undergo direct functionalization relatively easily, likely because of their weakness and the influence of a proximal aromatic system or a lone pair of electrons which can interact with the metal center. In comparison, the direct functionalization of unactivated C(sp^3)–H bonds remains underdeveloped and continues to be highly challenging because of the absence of

[144] For selected reviews on C(sp^2)–H functionalization, see: a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. b) D. –G. Yu, B. –J. Li, Z. –J. Shi, *Tetrahedron* **2012**, *68*, 1885. c) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740. d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147. e) O. Daugulis, H. –Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074. f) X. Chen, K. M. Engle, D. –H. Wang, J. –Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. g) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174. h) M. Tobisu, N. Chatani, *Angew. Chem. Int. Ed.* **2006**, *45*, 1683. i) L. –C. Campeau, K. Fagnou, *Chem. Commun.* **2006**, 1253. j) B. A. Arndtsen. R. G. Begman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **1995**, *28*, 154. For asymmetric catalytic carbon-carbon coupling reactions via C–H bond activation, see: k) L. Yang, H. Huang, *Catal. Sci. Technol.* **2012**, *2*, 1099.

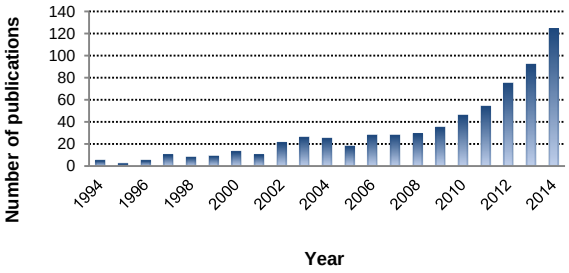
[145] For selected recent examples on allylic C(sp^3)–H functionalization, see: [Amination]; a) I. I. Strambeanu, M. C. White, *J. Am. Chem. Soc.* **2013**, *135*, 12032. b) C. Jiang, D. J. Covell, A. F. Stepan, M. S. Plummer, M. C. White, *Org. Lett.* **2012**, *14*, 1386. [Alkoxylation]; c) S. A. Ammann, G. T. Rice. M. C. White, *J. Am. Chem. Soc.* **2014**, *136*, 10834. d) T. J. Osberger, M. C. White, *J. Am. Chem. Soc.* **2014**, *136*, 11176. [Alkylation]; e) J. M. Howell, W. Liu, M. C. White, *J. Am. Chem. Soc.* **2014**, *136*, 5750. f) A. J. Young, M. C. White, *Angew. Chem. Int. Ed.* **2011**, *50*, 6824.

[146] For selected recent publications on benzylic C(sp^3)–H functionalization, see: a) B. Qian, S. Guo, J. Shao, Q. Zhu, L. Yang, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2010**, *132*, 3650. b) P. M. Burton, J. A. Morris, *Org. Lett.* **2010**, *12*, 5359. c) D. J. Schipper, L. –C. Campeau, K. Fagnou, *Tetrahedron*, **2009**, *65*, 3155. d) T. Niwa, H. Yorimitsu, K. Oshima, *Org. Lett.* **2008**, *10*, 4689. e) J. J. Mousseau, A. Larivée, A. B. Charette, *Org. Lett.* **2008**, *10*, 1641. f) L. –C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266.

[147] For reviews on acidic C(sp^3)–H bonds functionalization α- to electron-withdrawing groups, see: a) C. C. C. Johansson, T. J. Colacot, *Angew. Chem. Int. Ed.* **2010**, *49*, 676. b) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082. For a review on C(sp^3)–H functionalization α to hydroxy and ether moieties, see: c) S. –Y. Zhang, F. –M. Zhang, Y. –Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937.

stabilizing orbital interactions with the metal center, as in the case of unsaturated hydrocarbons.[148,149] To overcome the important challenges associated to the C(sp^3)–H activation, the use of removable directing groups has emerged as the preferred strategy to promote both reactivity and selectivity. Owing to its outstanding reactivity, controllable selectivity and its compatibility with a broad scope of directing groups, compared to other transition metals, most remarkable progress in this research field has been accomplished with palladium catalysis. In particular, coordination-directed C–H bond functionalization of nitrogen-containing compounds, such as amino acid derivatives, stands at the forefront of C(sp^3)–H activation, given their prevalence in natural products. Hence, we mainly will focus on the β- or γ-functionalization of α-amino acids *via* palladium-catalyzed C(sp^3)–H activation.[150]

[148] In spite of the difficulties associated with this class of unactivated substrates, notorious improvements have been achieved in C(sp^3)–H functionalization in last years. As depicted in the Figure below, an exponential increase in the number of metal-catalyzed C(sp^3)–H publications reported in the literature has been observed. The number of publications on the topic C(sp^3)–H functionalization was obtained by a SciFinder search using key words "C(sp^3)–H activation", categorized by "synthetic chemistry-reactions" and "catalysis".

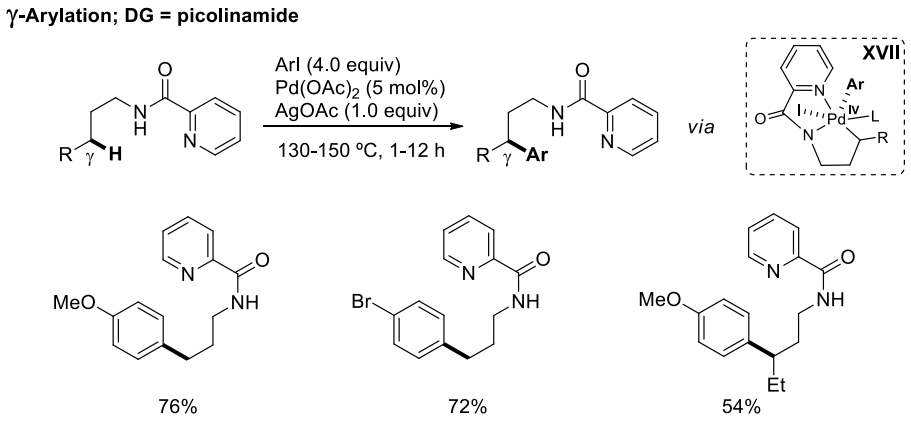


[149] For selected reviews on C(sp^3)–H bonds functionalization, see: a) O. Baudoin, *Chem. Soc. Rev.* **2011***, 40*, 4092. b) H. Li, B. –J. Li, Z. –J. Shi, *Catal. Sci. Technol.* **2011**, *1*, 191. c) M. Wasa, K. M. Engle, J. –Q. Yu, *Isr. J. Chem.* **2010**, *50*, 605. d) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654. e) J. –Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041. f) R. H. Crabtree, *J. Organomet. Chem.* **2004**, *689*, 4083.

[150] For a recent specific review on C–H functionalization in the synthesis of amino acids and peptides, see: A. F. M. Noisier, M. A. Brimbler, *Chem. Rev.* **2014**, *114*, 8775.

- ***Arylation / Alkenylation***

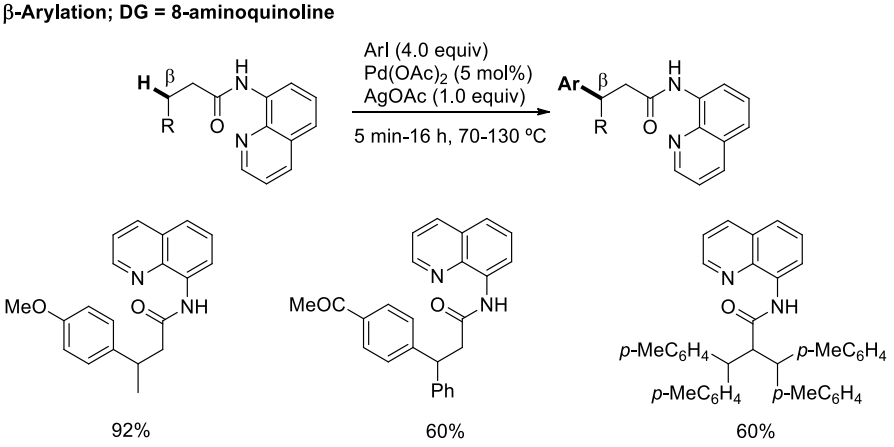
In 2005, Daugulis and co-workers reported a highly selective $Pd(OAc)_2$-catalyzed arylation of aliphatic C–H bonds using a (2-pyridyl)carbonylamino or picolinamide (PA) directing group as removable auxiliary.[151] For example, *N*-alkyl-picolinamides efficiently underwent regioselective arylation in the presence of catalytic $Pd(OAc)_2$ (5 mol%), stoichiometric AgOAc (1.0 equiv) and excess of the aryl iodide coupling partner (4.0 equiv) to yield the corresponding γ-arylated amine derivatives in moderate to good yields (54-81%). The γ-selectivity likely results from the formation of a kinetically favoured five-membered palladacycle intermediate (**XVII**) (Scheme 3.6). In the same report, the authors developed a method for the β-arylation of carboxylic acid derivatives using 8-aminoquinoline (AQ) as directing group (Scheme 3.7b).[152]



Scheme 3.6

[151] V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154.

[152] The efficient Pd^{II}-catalyzed arylation of methyl and also the more challenging methylene β-C(sp^3)–H bonds of amides was effective by employing an 8-aminoquinoline auxiliary. For other selected examples, see: a) F. Pan, P. –X. Shen, L. –S. Zhang, X. Wang, Z. –J. Shi, *Org. Lett.* **2013**, *15*, 4758. b) E. T. Nadres, G. I. F. Santos, D. Shabashov, O. Daugulis, *J. Org. Chem.* **2013**, *78*, 9689. c) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965.



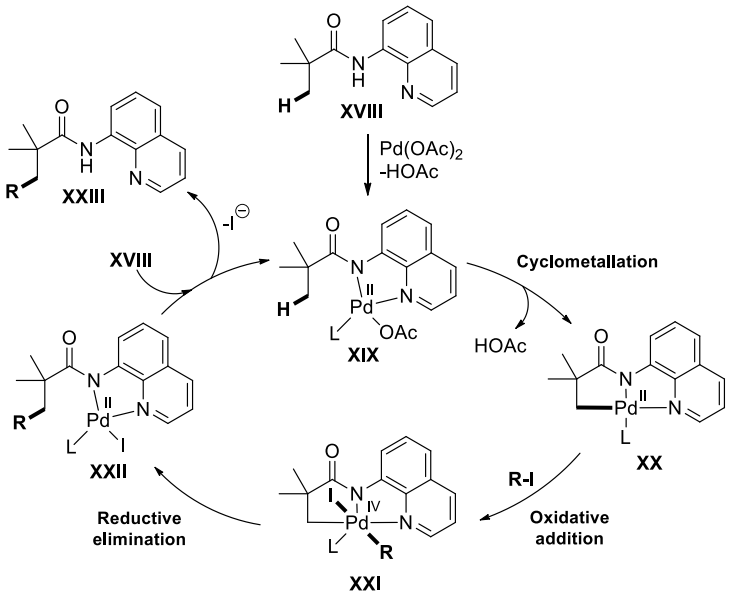
Scheme 3.7

The mechanism shown in Scheme 3.8 with *N*-(8-quinolyl)pivalamide (**XVIII**) as the parent substrate was proposed by Shabashov and Daugulis and involves a Pd^{II}/Pd^{IV} process.[153,154] The initial reaction of $Pd(OAc)_2$ with **XVIII** affords **XIX** by deprotonative *N*,*N*-coordination. A rapid cyclometallation of the *tert*-butyl group (C–H activation) would then take place to give the palladacycle **XX**. Oxidative addition of the aryl iodide to **XX** affords the Pd^{IV} species **XXI**. Reductive elimination followed by a

[153] For general recent reviews on Pd^{IV} chemistry, see: a) K. J. Bonney, F. Schoenebeck, *Chem. Rev.* **2014**, *43*, 6609. b) L. –M. Xu, B. –J. Li, Z. Yang, Z. –J. Shi, *Chem. Soc. Rev.* **2010**, *39*, 712. c) P. Sehnal, R. J. K. Taylor, I. J. S. Fairlamb, *Chem. Rev.* **2010**, *110*, 824. d) K. Muñiz, *Angew. Chem. Int. Ed.* **2009**, *48*, 9412. e) A. J. Hickman, M. S. Sanford, *Nature*, **2012**, *484*, 177. For a very recent study on Pd^{II}/Pd^{IV} mechanism, see: f) Y. Dang, S. Qu, J. W. Nelson, H. D. Pham, Z. –X. Wang, X. Wang, *J. Am. Chem. Soc.* **2015**, *137*, 2006. For a review on selective reductive elimination from high-valent metal centers with F^+ oxidants, see: g) K. M. Engle, T. –S. Mei, X. Wang, J. –Q. Yu, *Angew. Chem. Int. Ed.* **2011**. *50*, 1478. For a study on the carboxylate mediated reductive elimination from high-valent palladium species, see: h) J. B. Gary, M. S. Sanford, *Organometallics*, **2011**, *30*, 6143.

[154] Mechanistic investigations by Sandford and Ritter suggested a plausible bimetallic palladium(III) intermediate instead of the monometallic active palladium species commonly proposed, see: a) N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234. b) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 17050.

ligand exchange then releases the arylated product **XXIII** and regenerates the active palladium(II) species that reacts again with **XVIII** to afford the *N*,*N*-complex **XVIII**.

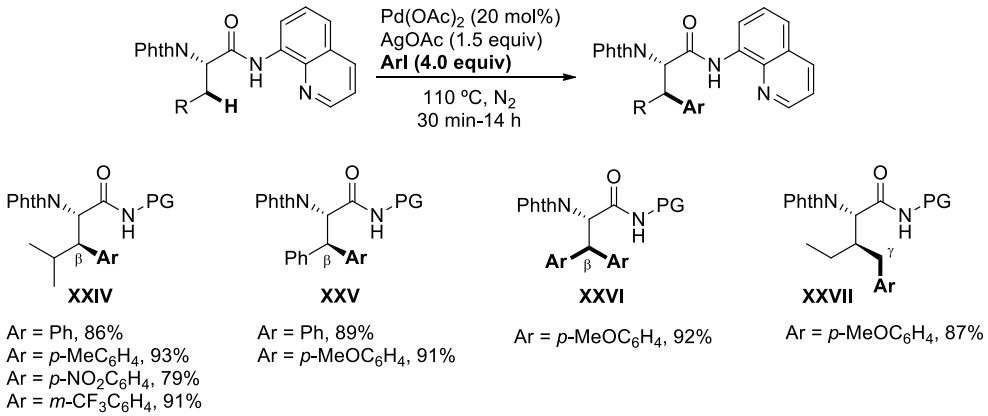


Scheme 3.8

Inspired by the efforts of Daugulis and co-workers, the group of Corey reported in 2006 the $Pd(OAc)_2$-catalyzed diastereoselective arylation of β-C(sp^3)–H bonds of α-amino acid derivatives (Scheme 3.9).[155] Under similar conditions to those previously reported, yet requiring higher catalyst loading [(20 mol% of $Pd(OAc)_2$)], a wide range of amino acid derivatives were efficiently arylated using aryl iodides derivatives (4.0 equiv). Amino acids presenting a secondary C(sp^3)–H bond in the β-position, such as leucine and phenylalanine (products **XXIV** and **XXV**, respectively), were successfully monoarylated with several aryl iodides, holding both electron-donating and -withdrawing substituents (79-93% yield). In the case of alanine, which exhibits a primary β-C(sp^3)–H bond, the monoarylation could not be controlled thus

[155] B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391.

rendering the diarylated derivative **XXVI** (92% yield). An interesting outcome was observed in the reaction of isoleucice with *p*-iodoanisole under similar reaction conditions. The unexpected arylation of the γ-C–H bond took place, thus indicating that the insertion of palladium into the bulky tertiary β-C–H bond is so attenuated that competitive γ-C–H bond activation can occur (compound **XXVII**, 87% yield).



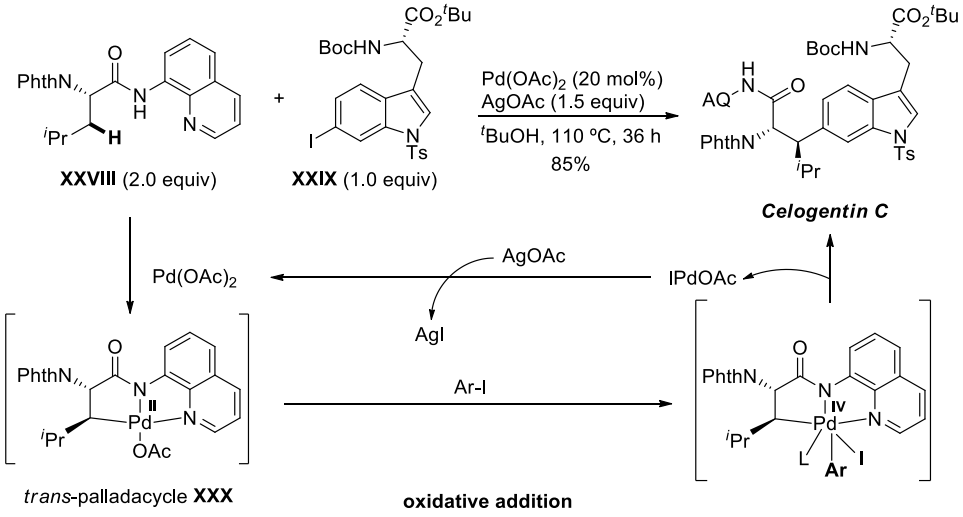
Scheme 3.9

These contributions allowed Feng and Chen to develop a strategy for the total synthesis of *Celogentin C*, a bicyclic non-ribosomal peptide that acts as an antimitotic agent by inhibiting Tubulin isomerization.[156] The authors were able to apply the 8-aminoquinoline-directed Pd^{II}-catalyzed C(sp^3)–H arylation reaction to form the key carbon–carbon bond connecting the *N*-phthaloyl leucine **XXVIII** with the 6-iodotryptophan derivative **XXIX** (Scheme 3.10). This achievement constitutes the first application of a metal-catalyzed C–H bond activation through formation of a bidentate chelate for the total synthesis of a natural product.[157] The high

[156] Y. Feng, G. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 958.

[157] For selected examples of subsequent application of C(sp^3)–H functionalization to the total synthesis of complex molecules, see: a) D. Dailler, G. Danoun, O. Baudoin, *Angew. Chem. Int. Ed.* **2015**, *54*, 4919. b) S. Guo, X. Zhang, P. Tang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4065. c) C. P. Ting, T. J. Maimone, *Angew. Chem. Int. Ed.* **2014**, *53*, 3115. d) W. R. Gutekunst, R. Gianatassio, P. S.

diastereoselectivity observed was proposed to arise from the coordination by the quinoline moiety, which promotes the formation of the *trans*-palladacycle intermediate **XXX**. Oxidative addition of the aryl iodide **XXIX** to **XXX** is then proposed to generate a Pd^{IV} intermediate which can reductively eliminate the expected product with concomitant catalyst regeneration *via* salt metathesis in the presence of AgOAc.



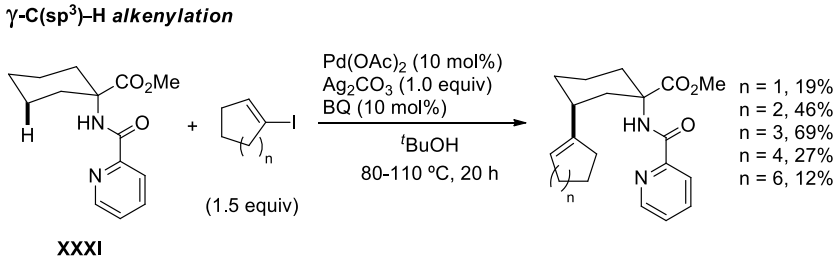
Scheme 3.10

Even though these precedents represent the first examples demonstrating the ability of a removable directing group [picolinamide (PA) or 8-aminoquinoline (AQ)] [158] facilitating the Pd-catalyzed direct C–H arylation of remote aliphatic positions, it was achieved at the cost of relatively demanding reaction conditions (generally 4.0 equiv of ArI at 110-150 ºC). In 2011, the group of Chen developed a milder method for the monoarylation of the γ-C(sp^3)–H bonds of a variety of aliphatic amines, including the

Baran, *Angew. Chem. Int. Ed.* **2012**, *51*, 7507. e) W. R. Gutekunst, P. S. Baran, *J. Am. Chem. Soc.* **2011**, *133*, 19076.

[158] For selected examples on the use of strongly deactivated poli-fluoro substituted amide derivates as auxiliary groups in the C(sp^3)–H arylation, see: a) M. Wasa, J. –Q. Yu, *Tetrahedron,* **2010**, *66*, 4811. b) M. Wasa, K. M. Engle, J. –Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 9886.

cyclohexylamino acid **XXXI**, using ^{t}BuOH or trifluoroethanol as the solvent at 80 ºC.[159] Disubstituted alkenyl iodides were also amenable with this protocol achieving the γ-alkenylated derivatives in poor to moderate yields (12-69%) (Scheme 3.11).[160] This method was applied to the synthesis of *(+)Obafluorin* from a readily accessible threonine derivative (Scheme 3.12). Since the removal of the picolinamide directing group was found to be challenging, the use of an *ortho*-silyloxymethyl analogue proved to be a viable alternative as it could be cleaved under mild acidic conditions.[161]

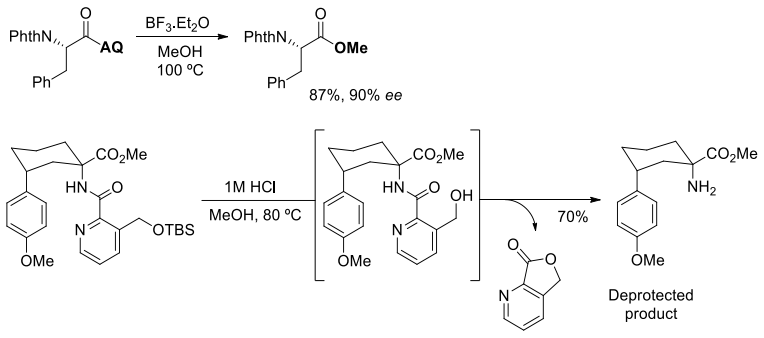


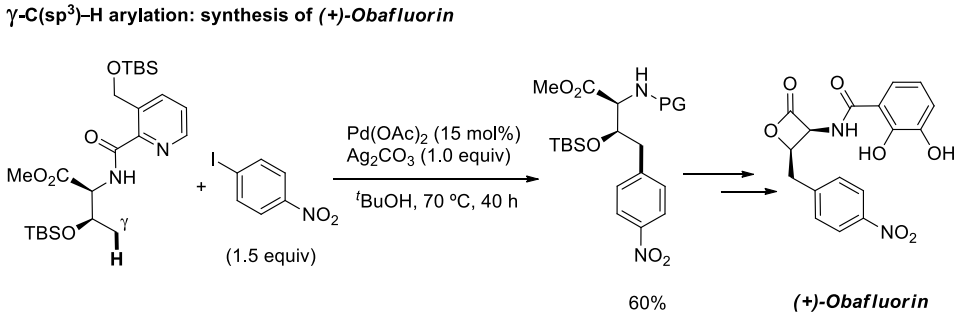
Scheme 3.11

[159] G. He, G. Chen, *Angew. Chem. Int. Ed.* **2011**, *50*, 5192.

[160] For other selected examples on palladium-catalyzed alkenylation of C(sp^3)–H bonds, see: a) [DG = amide derivatives]; M. Wasa, K . M. Engle, J. –Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680. b) [DG = pyridine]; K. J. Stowers, K. C. Fortner, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 6541.

[161] Classically, picolinamide or 8-aminoquinoline derivatives are deprotected upon their treatment with $BF_3{\cdot}Et_2O$ in refluxing MeOH. In contrast, the *ortho*-silyloxymethyl-modified picolinamide auxiliary can be hydrolyzed under milder acidic conditions due to the assistance of the hydroxyl group.



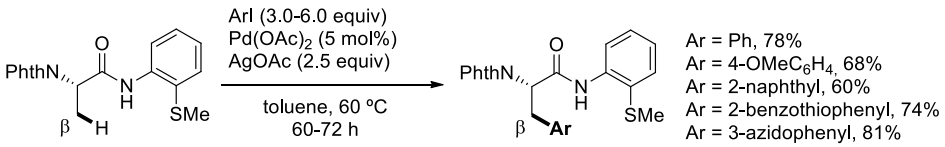


Scheme 3.12

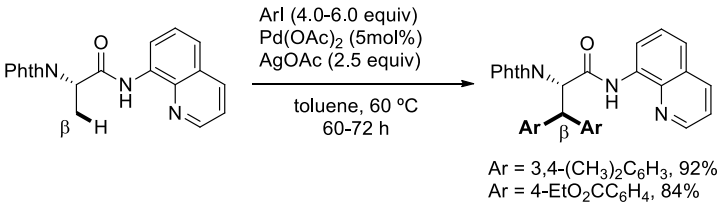
Building on their initial report, the group of Daugulis developed a method for the effective mono-arylation of primary β-C(sp^3)–H bonds of alanine derivatives with (hetero)aryl iodides that relies on the use of 2-methylthioaniline as directing group, which seems to be crucial for achieving good monoarylation selectivity (61-81% yield, Scheme 3.13a), as the 8-aminoquinoline auxiliary afforded diarylated alanine derivatives as major products (84-92% yield, Scheme 3.13b).[162] Additionally, a diastereoselective *anti*-arylation protocol for secondary methylene C(sp^3)–H bonds was also achieved when using 8-aminoquinoline as directing group (77-95% yield, *syn*/*anti* = 1:13-1:50, Scheme 3.13c).

[162] L. Dieu, O. Daugulis, *Angew. Chem. Int. Ed.* **2012**, *51*, 5188.

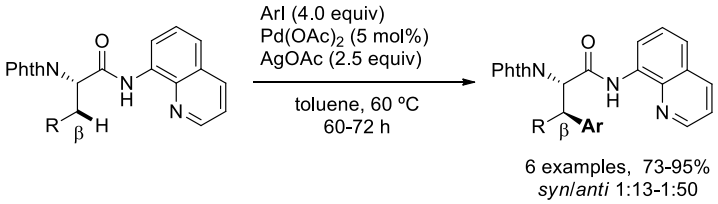
a) mono-Arylation of alanine derivative; DG = 2-thiomethylaniline



b) di-Arylation of alanine derivative; DG = 8-aminoquinoline



c) *anti*-Arylation of secondary β-C(sp^3)–H bonds; DG = 8-aminoquinoline



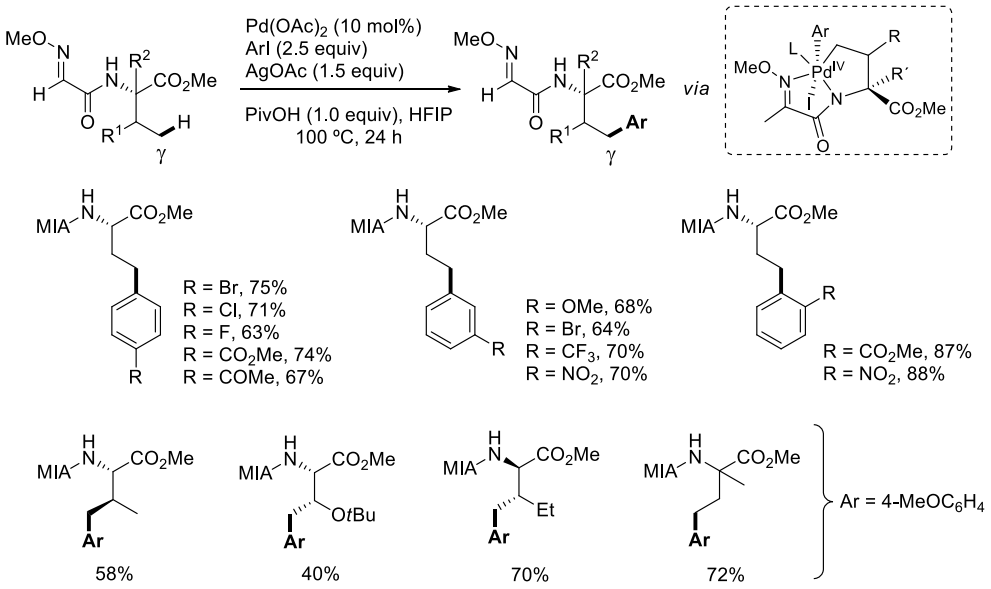
Scheme 3.13

Inspired by the work of Daugulis, several research groups, including ours, have focused their attention on the development of what has become a collection of new bidentate directing groups capable of functionalizing α-amino acids at aliphatic positions.[163] Among them, the group of Ma has reported a Pd-catalyzed γ-arylation of α-amino esters relying on the use of 2-methoxyiminoacetyl (MIA) as an alternative to the 8-aminoquinoline and 2-methylthioaniline directing groups.[164] Whereas $Pd(OAc)_2$ (10 mol%) and HFIP proved to be the catalyst and the solvent of choice, a

[163] For a recent review on the ligand control reactivity and selectivity in palladium-catalyzed functionalization of unactivated C(sp^3)–H bonds, see: M. A. Fernández-Ibáñez, *ChemCatChem.* **2014**, *6*, 2188.

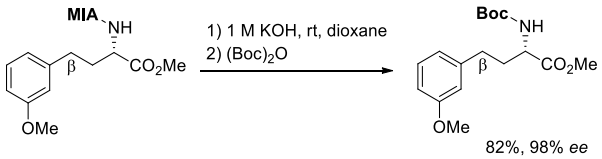
[164] M. Fan, D. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 12152.

combination of AgOAc (1.5 equiv) and PivOH (1.0 equiv) as additive, was found to be optimal. Under these reaction conditions a wide range of electronically different iodoarenes (2.5 equiv) were efficiently coupled at the γ-position of the MIA-modified homophenylalanine derivatives (Scheme 3.14). Remarkably, the method tolerated substitution of the aryl iodide at the *ortho*, *meta*- and *para*- positions (20 examples, 54-87% yield). Additionally, the reaction was successfully extended to the valine, threonine, allo-isolucine and α-methylhomoalanine analogues (40-72% yield).[165,166]



Scheme 3.14

[165] The MIA group can be removed by hydrolysis with 1 M KOH thus affording the free amine, which was subsequently subjected to Boc-protection.



[166] For the use of *O*-methyl hydroxamic acid as directing group in C(sp^3)–H arylation, see: D. –H. Wang, M. Wasa, R. Giri, J. –Q. Yu. *J. Am. Chem. Soc.* **2008**, *130*, 7190.

During the course of this project, other research groups have continued to exploit the great potential of the use of 8-aminoquinoline (AQ) directing group in the direct arylation of α-amino acids at the aliphatic β- and γ-positions.[167] On the other hand, the research group of Yu has recently reported elegant ligand-enabled C(sp^3)–H arylation of amino acid and peptide derivatives.[168,169]

- ***Alkylation***

Compared with the arylation or vinylation of aliphatic C–H bonds, the direct C–H alkylation remains underdeveloped.[170] A significant advance was made by the group of Daugulis in parallel with the Pd^{II}-catalyzed β-arylation of C(sp^3)–H bonds.[152c] They successfully expanded this method to the C–H alkylation with alkyl iodide or bromide partners (Scheme 3.15a). This transformation is remarkable, given the inherent resistance of alkyl halides toward oxidative addition and the tendency of the resulting alkyl-metal species to undergo β-hydride elimination. Soon after this pioneering report, the same research team reported the first example of C(sp^3)–H alkylation of

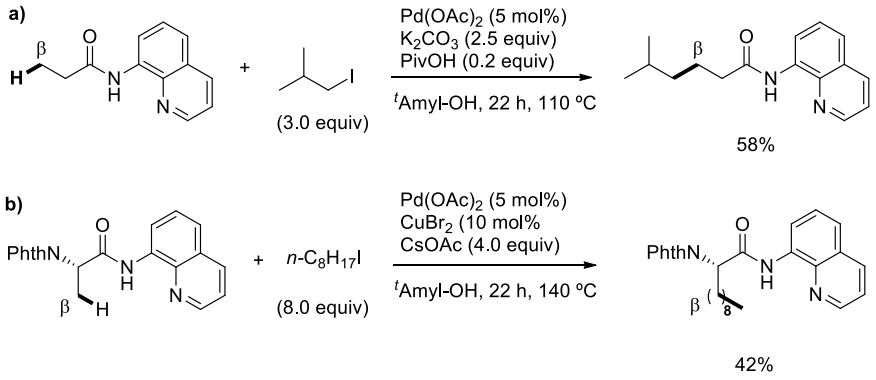
[167] The groups of Chen and Shi have simultaneously reported the *anti*-β-mono-arylation of alanine derivatives with a wide range of aryl iodides: a) B. Wang, W. A. Nack, G. He, S. –Y. Zhang, G. Chen, *Chem. Sci.* **2014**, *5*, 3952. b) K. Chen, S. –Q. Zhang, J. –W. Xu, F. Hu, B. –F. Shi, *Chem. Commun.* **2014**, *50*, 13924. For the *syn*-β-mono-arylation of pyrrolidine derivatives, see: c) D. P. Affron, O. A. Davis, J. A. Bull, *Org. Lett.* **2014**, *16*, 4956.

[168] For a recent site-selective C(sp^3)–H functionalization (arylation and acetoxylation) of di-, tri- and tetrapeptides, see: a) W. Gong, G. Zhang, T. Liu, R. Giri, J. –Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 16940. See also: b) J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J. –Q. Yu, *Science*, **2014**, *343*, 1216.

[169] For a very recent ligand enabled β-arylation of α-amino acid derivatives using a simple and practical auxiliary [CONHOMe], see: a) G. Chen, T. Shigenari, P. Jain, Z. Zhang, Z. Jin, J. He, S. Li, C. Mapelli, M. M. Miller, M. A. Poss, P. M. Scola, K. –S. Yeung, J. –Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 3338. For a recent ligand-enabled cross-coupling of C(sp^3)–H bonds with arylboron reagents *via* Pd^{II}/Pd^0 catalysis, see: b) K. S. L. Chan, M. Wasa, L. Chu, B. N. Laforteza, M. Miura, J. –Q. Yu, *Nature Chem*. **2014**, *6*, 146, c) M. Wasa, K. S. L. Chan, X. –G. Zhang, J. He, M. Miura, J. –Q. Yu. *J. Am. Chem. Soc.* **2012**, *134*, 18570.

[170] For a review on metal-catalyzed direct alkylation of (hetero)arenes *via* C–H bond cleavage, see: L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866.

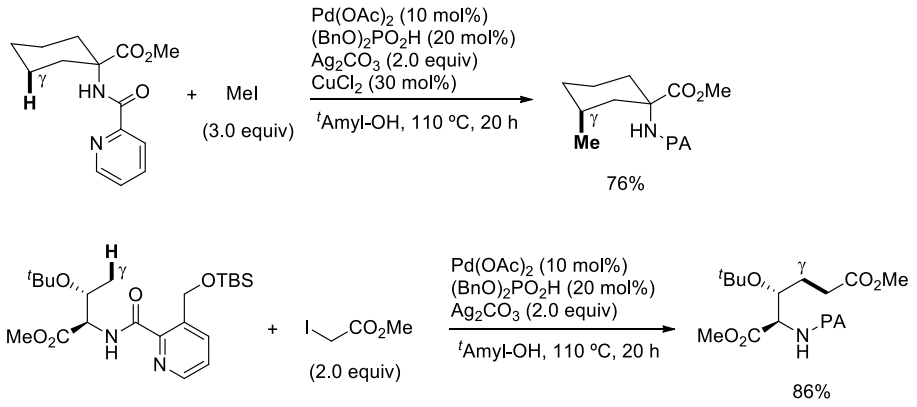
amino acid derivatives under slightly modified conditions.[152b] The reaction of *N*-phthaloylalanine derivatized bearing the 8-aminoquinoline directing group with 1-iodooctane was performed using $Pd(OAc)_2$ (5 mol%) and $CuBr_2$ (10 mol%) in combination with CsOAc as base (4.0 equiv) as base, affording the desired alkylated product in 42% yield (Scheme 3.15b).



Scheme 3.15

Inspired by these pioneering examples, in 2013 Chen and co-workers published the γ- and δ-C(sp^3)–H alkylation of picolinamide(PA)-protected aliphatic amines with primary alkyl iodides (Scheme 3.16).[171] Interestingly, the reaction reached its optimum efficiency when a silver salt was used together with an organic phosphate additive: $(BnO)_2PO_2H$. Various linear primary alkyl iodides were described as efficient alkylating agents and the reaction tolerated a large diversity of amine backbones, including α-amino acids.

[171] a) S. Y. Zhang, G. He, W. A. Nack, Y. Zhao, Q. Li, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 2124. For a stereoselective synthesis of β-alkylated α-amino acid derivatives *via* palladium-catalyzed alkylation of unactivated methylene C(sp^3)–H bonds with primary alkyl halides using picolinamide (PA) as directing group, see: b) S. –Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135.



Scheme 3.16

Almost simultaneously, Shi (2013) reported a milder protocol for the C(sp^3)–H alkylation of amino acid derivatives functionalized with the 8-aminoquinoline (AQ) directing group.[172] Shi´s optimized reaction conditions [$Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (0.8 equiv), $(BnO)_2PO_2H$ (0.3 equiv),[173] RI (1.5 equiv), in a DCE/^{t}BuOH (1:1) mixture at 50 ºC for 2 h] promoted the coupling of a wide range of primary alkyl iodides, encompassing various size chains from methyl iodide to $C_{18}H_{37}I$, yielding the expected products in moderate to good yields (25-87%, Scheme 3.17a). Alkyl iodides bearing functional groups such as halides, protected amines, carboxylic esters or alkanes were compatible with this protocol. However, secondary alkyl iodides remained unreactive under these reaction conditions. Interestingly, alkyl bromides, which are less expensive and more readily available, factors that make them attractive in both academia and industry, were well tolerated albeit requiring slightly harsher reaction conditions (90 ºC, 24 h) and increased amounts of RBr (3.0 equiv).

[172] K. Chen, F. Hu, S. –Q. Zhang, B. –F. Shi, *Chem. Sci*. **2013**, *4*, 3906.

[173] The $(BnO)_2PO_2H$ additive was proposed to enable a better control of the concentration of Ag^+ in solution, thus playing a key role in the oxidative addition step. The Ag^+ cations may not only act as halide scavengers necessary for high turnover of the catalytic cycle, but also their Lewis acidity might enhance the electrophicity of the alkyl iodides. On the other hand, increased concentrations of Ag^+ in solution might lead to decomposition of the alkyl iodides through a E2 elimination.

Differently alkylated derivatives were achieved in moderate to good yields (16-79%). In addition the authors also achieved the alkylation of secondary β-C(sp^3)–H bonds of various amino acid derivatives with α-iodoacetate esters and α-bromoacetate esters in good yields and excellent *anti*-diastereoselectivities (44-91, >50:1 dr, Scheme 3.17b).[174,175] Finally, when valine derivative, presenting a tertiary C(sp^3)–H bond in the β-position, was subjected to the optimized reactions conditions, the γ-alkylated product was achieved in 41% yield and 17:1 dr (Scheme 3.18). The authors proposed that the C–H activated Pd^{II} complex attack to the α-haloacetate could follow a S_N2 mechanism, where the later one would be activated due to the presence of silver counter ions, generating a high-valent Pd^{IV} intermediate, which after reductive elimination would release the expected product.[176,177]

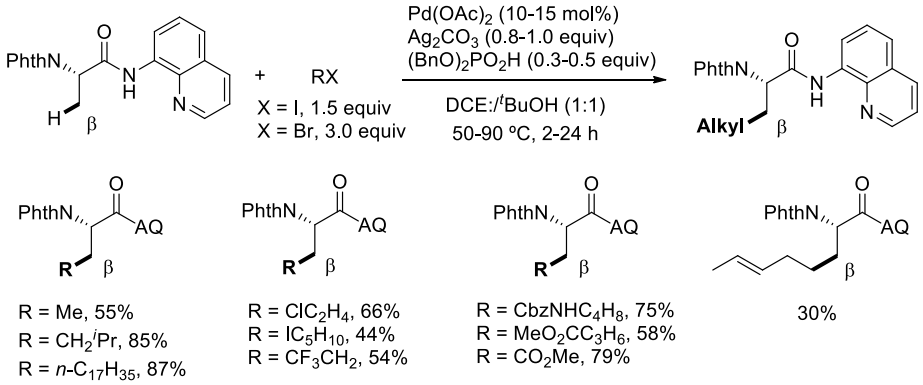
[174] For a sulfonamide promoted stereoselective alkylation of unactivated methylene C(sp^3)–H bonds of α-amino acid derivatives with primary alkyl halides using 8-aminoquinoline (AQ) as directing group, see: a) K. Chen, B. –F. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 11950. For other selected example on the alkylation of unactivated C(sp^3)–H bonds, see: [PG = pyridine]; b) B. –F. Shi, N. Maugel, Y. –H. Zhang, J. –Q. Yu, *Angew. Chem. Int. Ed.* **2008**, *47*, 4882.

[175] For other metal-catalyzed alkylation of unactivated C(sp^3)–H bonds, see: [Iridium]; a) S. Pan, Y. Matsuo, K. Endo, T. Shibata, *Tetrahedron* **2012**, *68*, 9009. b) S. Pan, K. Endo, T. Shibata, *Org. Lett.* **2011**, *13*, 4692. [Nickel] c) X. Fu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.* **2014**, *136*, 1789. [Ruthenium]; d) A. A. Kulago, B. F. Van Steijvoort, E. A. Mitchell, L. Meerpoel, B. U. W. Maes, *Adv. Synth. Catal.* **2014**, *356*, 1610.

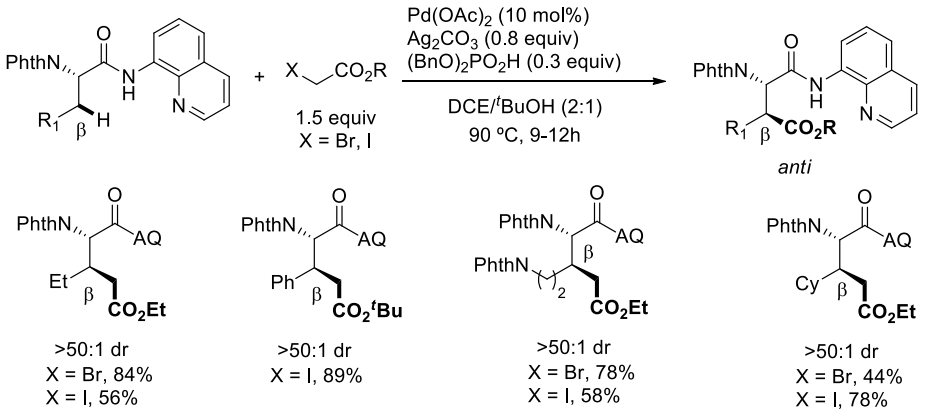
[176] During the course of our investigations, Yu reported a new protocol for the alkylation of C(sp^2)–H, vinylic C–H and unactivated C(sp^3)–H bonds with a wide range of alkyl iodides. The use of *N*-phthaloyl derivatives bearing the weakly coordinating 2,3,5,6-tetrafluoro-4-trifluoromethylaniline auxiliary in conjuction with 9-methylacridine as ligand resulted crucial for the success of the reaction, see: R. –Y. Zhu, J. He, X. –C. Wang, J. –Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 13197.

[177] The alkynylation of unactivated C(sp^3)–H bonds has also been reported. However, these recent protocols have not been yet applied to the functionalization of amino acids derivatives. For selected examples, see: [DG = 8-aminoquinoline]; a) M. Al-Amin, M. Arisawa, S. Shuto, Y. Ano, M. Tobisu, N. Chatani, *Adv. Synth. Catal.* **2014**, *356*, 1631. b) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984. [DG = –CONH(4-CF_3)C_6F_4]; c) J. He, M. Wasa, K. S. L. Chan, J. –Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 3387. For a very recent gold photoredox example, see: d) J. Xie, S. Shi, T. Zhang, N. Mehrkens, M. Rudolph, A. Stephen, K. Hashmi, *Angew. Chem. Int. Ed.* **2015**, DOI: 10.1002/anie.201412399.

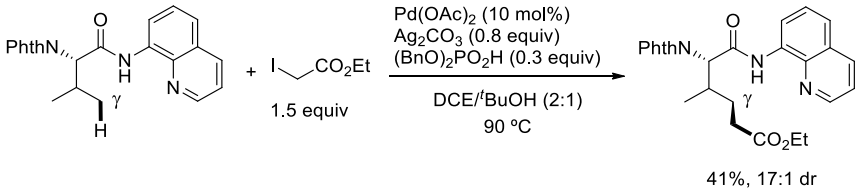
a) Alkylation of β–primary C(sp^3)–H bonds



b) Alkylation of β–secondary C(sp^3)–H bonds



Scheme 3.17



Scheme 3.18

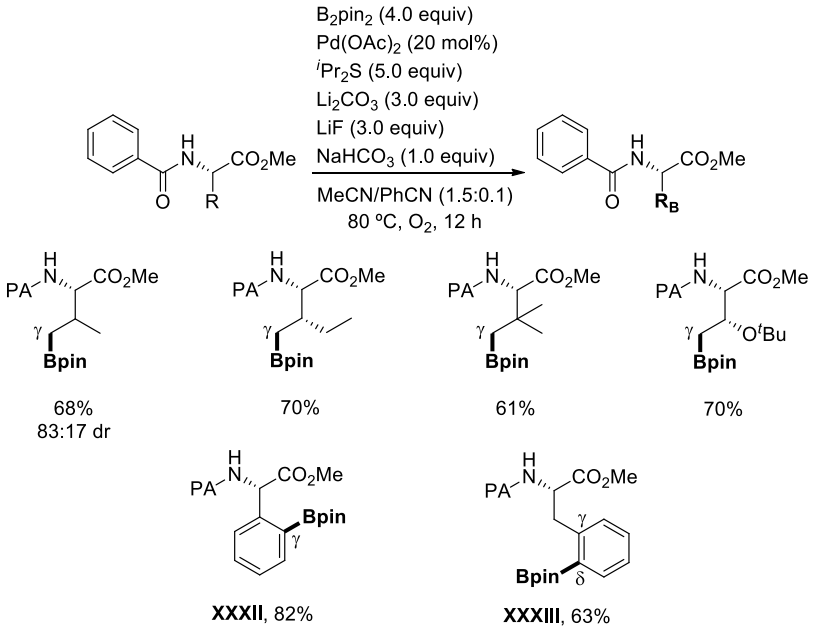
- ***Borylation***

In 2011 Zhang reported the challenging palladium-catalyzed borylation of amino acid derivatives using picolinamide (PA) as directing group (Scheme 3.19).[178] Although borylated compounds are important precursors *en route* to more complex molecules *via* Miyaura-Suzuki coupling, this same reactivity has hampered the development of palladium-catalyzed C–H borylation reactions. As an additional difficulty, the alkyl boronate ester formed could be oxidized in the presence of the stoichiometric oxidant necessary for the completion of the Pd-catalytic cycle.[179] Under the optimized reaction conditions; [$Pd(OAc)_2$ (20 mol%), B_2pin_2 (4.0 equiv), $^iPr_2S$ (5.0 equiv), Li_2CO_3 (3.0 equiv), LiF (3.0 equiv), $NaHCO_3$ (1.0 equiv), in a MeCN/PhCN (1.5:0.1) mixture at 80 ºC for 12 h under molecular oxygen atmosphere], a wide range of amino acid derivatives could efficiently be γ-borylated with good yields and diastereoisomeric ratios (41-84% yield, 83:17->20:1). While $^iPr_2S$ resulted to be a crucial ligand in order to prevent the precipitation of the catalyst in the form of deactivated palladium black, the weak base Li_2CO_3 promoted the formation of the expected borylated product without enhancing its reactivity towards Suzuki side-reactions. Interestingly, while other oxidants failed likely due to the sensitivity of boron toward oxidation, using O_2 as terminal oxidant efficiently regenerated the palladium active catalyst. Isoleucine, *tert*-leucine, *O*-*tert*-butyl threonine were γ-mono-borylated under the optimized reaction conditions (61-84% yield). This method was also found to be applicable to the C(sp^2)–H functionalization of aromatic amino acids. For example, the borylation of arylglycine under the optimized reaction conditions afforded the *ortho*-borylated derivative **XXXII** (γ-C–H activation) in 82% yield, while in

[178] L. –S. Zhang, G. Chen, X. Wang, Q. –Y. Guo, X. –S. Zhang, F. Pan, K. Chen, Z. –J. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 3899.

[179] For a comprenhensive review on iridum and rhodium-catalyzed C(sp^3)–H borylation until 2011, see: a) J. F. Hartwig, *Chem. Soc. Rev.* **2011**, *40*, 1992. For recent publications on the C(sp^3)–H borylation, see: [Rhodium]; b) T. Iwai, R. Murakami, T. Harada, S. Kawamorita, M. Sawamura, *Adv. Synth. Catal.* **2014**, *356*, 1563. [Iridium]; c) C. W. Liskey, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 3375. d) S. Kawamorita, R. Murakami, T. Iwai, M. Sawamura, *J. Am. Chem. Soc.* **2013**, *135*, 2947. e) T. Ohmura, T. Torigoe, M. Suginome, *J. Am. Chem. Soc.* **2012**, *134*, 17416. f) C. W. Liskey, J. F. Hartwig, *J. Am. Chem. Soc.* **2012**, *134*, 12422.

the case of phenylalanine **XXXIII** the C–H activation occurred at the remote δ-C(sp^2)–H bond (63% yield) due to the absence of a γ-C–H bond.



Scheme 3.19

- ***Acetoxylation / Alkoxylation***

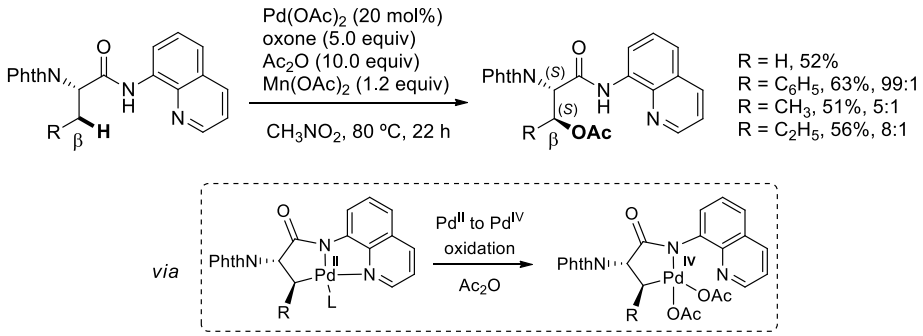
Soon after the 8-aminoquinolyl directing group which was originally introduced by Daugulis, Corey and co-workers reported a $Pd(OAc)_2$-catalyzed procedure for incorporating an oxygen atom into the β-C(sp^3)–H bond of α-amino acids, thus leading to β-hydroxy-α-amino acid derivatives (Scheme 3.20).[180] Among the different carboxamide directing groups tested, such as *N*-methoxyamide, Weinreb amide, oxazoline, picolinamide, pyridine-2-ylmethanamine or 8-aminoquinoline, only the 8-aminoquinoline group (AQ) provided good results. AQ-protected leucine, alanine, homoalanine, norvaline and phenylalanine were successfully β-acetoxylated in good

[180] B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391.

yields (51-63%) with good diastereoselectivities (*S*,*S*/*S*,*R* = 5:1-99:1). Interestingly, a combination of oxone (5.0 equiv) and $Mn(OAc)_2$ (1.2 equiv) seemed to be crucial for achieving optimal results. The authors postulated that $Mn(OAc)_2$ could be oxidized to $Mn_3O(OAc)_7$, which could act as a Lewis acid increasing the Pd electrophilicity, thus facilitating its insertion into the C–H bond. In addition to the double-five-membered palladacycle formed by the bidentate chelating nature of the 8-aminoquinoline directing group, previously postulated by Daugulis to explain the extremely difficult activation of the β-secondary C(sp^3)–H bond,[151] Corey suggested that the diastereoselectivity of the reaction could be the result of the sterically preferred formation of a *trans*-palladacycle where the *N*-Phth and the R groups adopt a *trans*-orientation.[181,182]

[181] For mechanistic insights on the palladium-catalyzed acetoxylation, see: a) L. Guo, Y. Xu, X. Wang, W. Liu, D. Lu, *Organometallics,* **2013**, *32*, 3780. b) B. Lian, L. Zhang, G. A. Chass, D. -C. Fai, *J. Org. Chem.* **2013**, *78*, 8376.

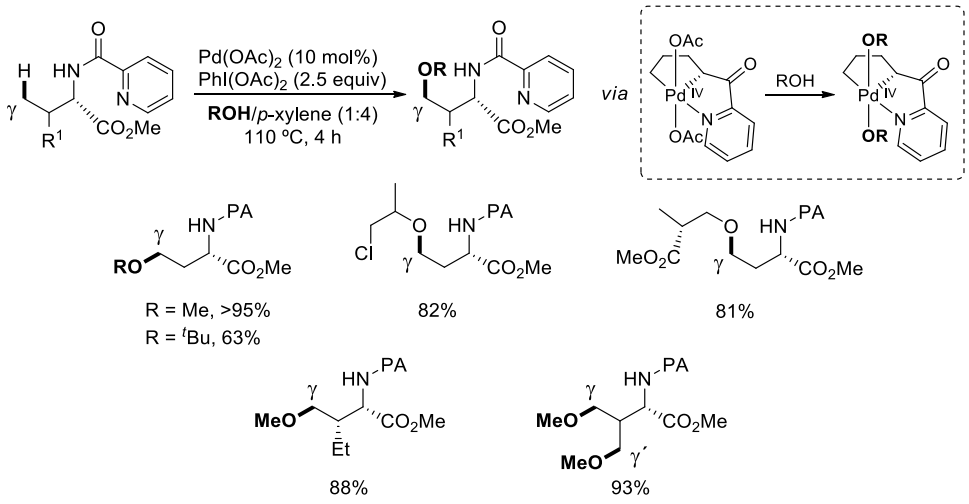
[182] For other selected examples on palladium-catalyzed C(sp^3)–H acetoxylation, see: [DG = oxime derivatives]; a) Z. Ren, F. Mo, G. Dong, *J. Am. Chem. Soc.* **2012**, *134*, 16991. b) K. J. Stowers, A. Kubota, M. S. Sanford, *Chem. Sci.* **2012**, *3*, 3192. c) S. R. Neufeldt, M. S. Sanford, *Org. Lett.* **2010**, *12*, 532. d) L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141. e) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542. [DG = oxazoline derivatives]; f) R. Giri, J. Liang, J. –G. Lei, J.- J. Li, D. –H. Wang, X. Chen, I. C. Naggar, C. Guo, B. M. Foxman, J. –Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 7420. [DG = Boc]; g) D. –H. Wang, X. –S. Hao, D. –F. Wu, J. –Q. Yu, *Org. Lett.* **2006**, *8*, 3387. [DG = picolinamide]; h) Q. Li, S. –Y. Zhang, G. He, W. A. Nack, G. Chen, *Adv. Synth. Catal.* **2014**, *356*, 1544. [DG = pyridylsulfoximide]; i) R. K. Rit, R. Yadav, A. K. Sahoo, *Org. Lett.* **2012**, *14*, 3724. [DG = PIP, -$C(CH_3)_2$Py]; j) F. –J. Chen, S. Zhao, F. Hu, K. Chen, Q. Zhang, S. –Q. Zhang, B. –F. Shi, *Chem. Sci.* **2013**, *4*, 4187. For the C(sp^3)–H acetoxylation of simple amides, see: k) L. Zhou, W. Lu, *Org. Lett.* **2014**, *16*, 508.



Scheme 3.20

More recently, in 2012, Chen developed a highly efficient method for the synthesis of alkyl ethers via Pd-catalyzed intermolecular alkoxylation of truly unactivated γ-C(sp^3)–H and δ-C(sp^2)–H bonds with a wide range of alcohols using picolinamide (PA) as directing group under oxidative conditions (Scheme 3.21).[183] Amino acid derivatives were also suitable substrates for the alkoxylation reaction under the optimized reaction conditions [$Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (2.5 equiv) in a ROH/*p*-xylene (1:4 mixture) under inert atmosphere at 110 ºC for 4 h]. The introduction of primary, secondary and even tertiary alcohols, including ^{t}BuOH, occurred efficiently. Additionally, a high regioselective preference for primary over secondary γ-C(sp^3)–H bonds was observed. Although the reaction mechanism was not firmly established, the authors proposed a Pd^{II}/Pd^{IV} mechanism where the acetate ligands are displaced by the alcohol (solvent) *via* a S_N2 pathway.

[183] S. –Y. Zhang, G. He, Y. Zhao, K. Wright, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 7313.

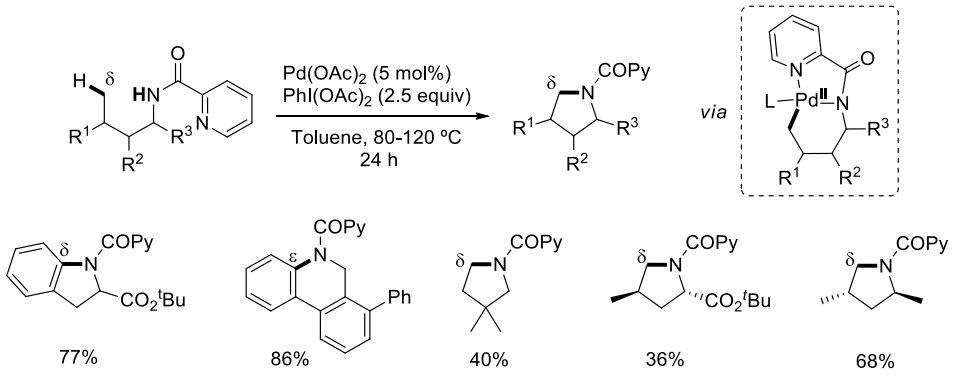


Scheme 3.21

- ***Amination/Amidation***

A rare direct Pd-catalyzed intramolecular amination not involving nitrene intermediates for the construction of nitrogen heterocycles was reported by Nadres and Daugulis in 2012 (Scheme 3.22).[184] The method made use of a picolinamide (PA) directing group and was applicable to δ-C(sp^2)–H as well as to aliphatic and benzylic δ-C(sp^3)–H bonds. Not only five-membered rings but also 6-membered rings can be formed with this method (ε-functionalization), thus demonstrating the potential participation of seven-membered palladacycles intermediates. The cleavage of the picolinamide auxiliary was realized using $LiEt_3BH$, which resulted in the formation of a pyrrolidine (or) piperidine bearing a secondary nitrogen function as the final product.

[184] E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7.

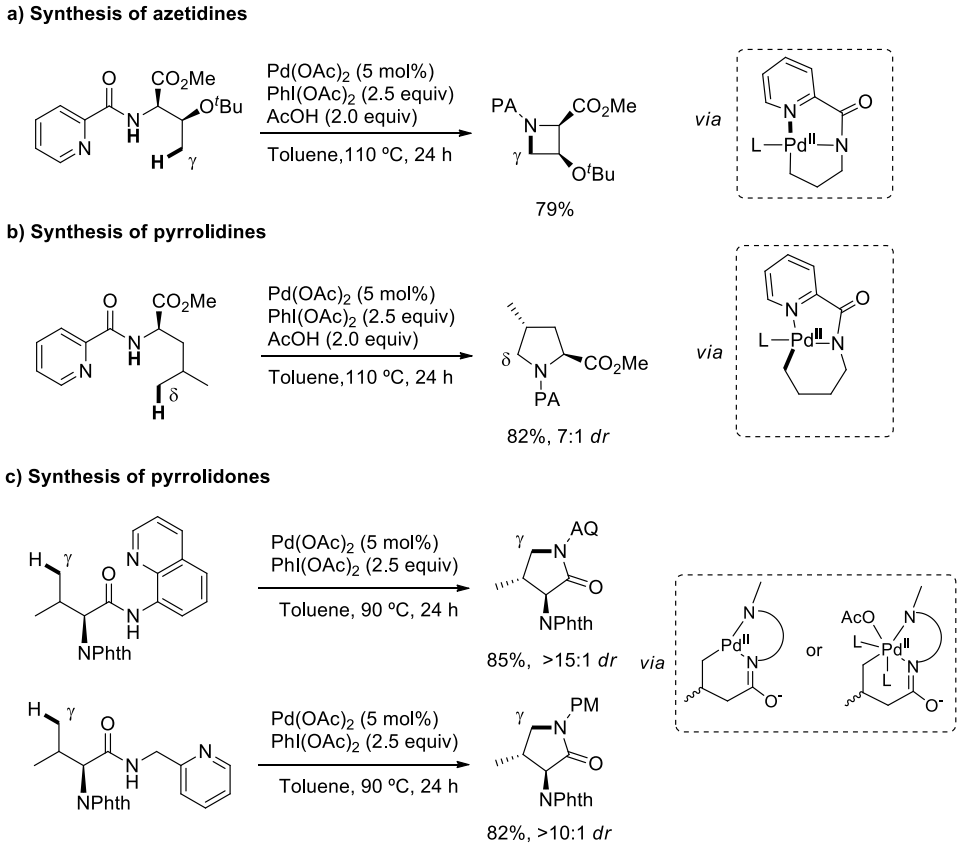


Scheme 3.22

An analogous method was simultaneously published by Chen and co-workers.[185] The Pd-catalyzed intramolecular amination of primary C(sp^3)–H at the γ-position of picolinamide-protected amine substrates allowed the seemingly unfavourable four-membered azetidine to be obtained using $PhI(OAc)_2$ (2.5 equiv) as the oxidant (Scheme 3.23a). Indeed, the activation of the γ-C(sp^3)–H bond to give a four-membered cycle seems to be preferred over the activation of the δ-C(sp^3)–H bond to give a five-membered ring. It was proposed that the formation of a six-membered palladacycle intermediate, which leads to five-membered ring, is likely to be kinetically less favoured. However, the method was applicable to the cyclization to give the pyrrolidine derivative if the C–H bond at the γ-position is bulky as a result of branching at the γ-position (Scheme 3.23b). Yields and diastereoselectivities were usually high when 2.0 equiv of AcOH were used. Of note, access to pyrrolidinones through γ-activation of carboxylic acid derivatives, including α-amino acids, required the use of either 8-aminoquinoline (AQ) or 2-pyridylmethylamine (PM) as the directing groups (Scheme 3.23c).[186]

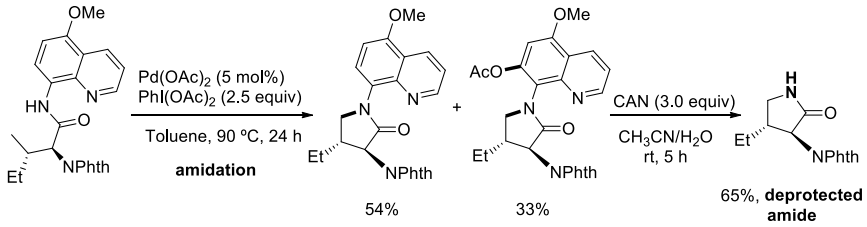
[185] a) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3. See also: b) G. He, S. –Y. Zhang, W. A. Nack, Q. Li, G. Chen, *Angew. Chem. Int. Ed.* **2013**, *52*, 11124.

[186] The authors also addressed the critical issue regarding the removal of the auxiliary group under relatively mild reaction conditions. They found that 8-amino-5-methoxyquinoline (MQ) could smoothly



Scheme 3.23

be removed in the presence of CAN (3.0 equiv) in a CH_3CN/H_2O mixture at rt for 5 h to give the primary amide and the quinone by-product.

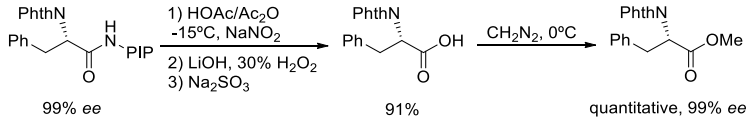


In 2013, Shi developed a very elegant method for the stereoselective synthesis of chiral α-amino-β-lactams through a sequential monoarylation/amidation of alanine derivatives.[187] As part of their study on the development of a C–H functionalization strategy for the synthesis of *N*-heterocycles, the authors employed the 2-(pyridine-2-yl)-isopropylamine (PIP) as an alternative to the picolinamide (PA) or 8-aminoquinoline (AQ) groups to achieve the selective monoarylation of the β-primary C(sp^3)–H bond of alanine derivative **XXXIV**, followed by intramolecular amidation of the resulting β-secondary C(sp^3)–H bond. Their sequential approach to α-amino-β-lactams is depicted in Scheme 3.24. The PIP directing group was able to afford the monoarylated products in high selectivity during the first reaction step while being stable to the oxidation conditions employed during the intramolecular amidation step.[188] A wide range of aryl iodides and even heteroaryl iodides were successfully applied, yielding phenylalanine derivatives in high yields and excellent selectivity. However, the use of aryl bromides failed to deliver the expected products. Finally, the PIP directing group could be cleaved through a mild *N*-nitrosation/hydrolysis sequence following esterification without loss of *ee*.[189,190]

[187] Q. Zhang, K. Chen, W. Rao, Y. Zhang, F. –J. Chen, B. –F. Shi, *Angew. Chem. Int. Ed.* **2013**, *52*, 13588.

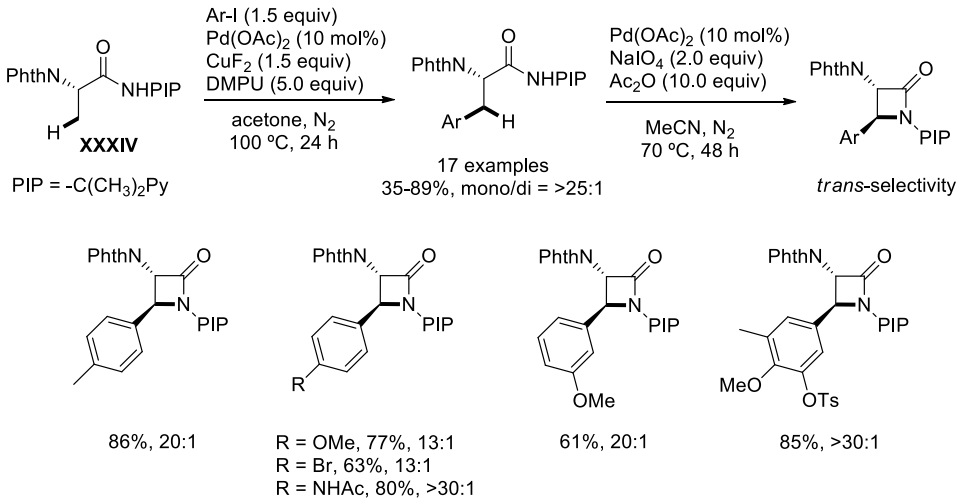
[188] In this amidation step, a combination of $NaIO_4$ and Ac_2O was proposed to be crucial for a slow release of $IO_{4-n}(OAc)_{2n-1}$, which would oxidize the key cyclopalladated Pd^{II} intermediate to a high valent Pd^{IV} species, promoting the C–N reductive elimination.

[189] The PIP-deprotection was achieved through the following sequence:



99% *ee* 91% quantitative, 99% *ee*

[190] For other examples on palladium-catalyzed intramolecular amination of C(sp^3)–H bonds, see: a) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129. b) W, -W. Sun, P. Cao, R. –Q. Mei, Y. Li, Y. –L. Ma, B. Wu, *Org. Lett.* **2014**, *16*, 480. c) J. J. Neumann, S. Rakshit, T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* **2009**, *48*, 6892. For a copper-catalyzed intramolecular amination using 8-aminoquinoline as directing group, see: d) X. Wu, Y. Zhao, G. Zhang, H. Ge, *Angew. Chem. Int. Ed.* **2014**, *53*, 3706. For selected examples on palladium-catalyzed intermolecular amination of C(sp^3)–H bonds, see: e) J. He, T. Shigenari, J. –Q. Yu. *Angew. Chem. Int. Ed.* **2015**, DOI:



Scheme 3.24

3.5. Palladium-catalyzed carbonylation of C(sp^3)–H bonds

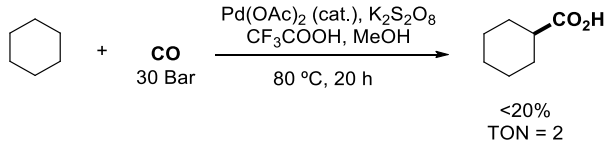
Palladium-catalyzed carbonylation reactions are widely recognized as a very important tool in both industrial and organic chemistry for the transformation of bulk chemicals or organic molecules into more precious products. This transformation allows the direct synthesis of carbonyl compounds using a readily available feedstock such as carbon monoxide (CO), which is also the simplest C-1 unit and meets the requirements of "atom economy" and "*Green Chemistry*".[3] The basic of this transformation were established in the mid-1970s by the pioneering work of Heck ad co-workers who described the reaction of vinyl and aryl halides with carbon monoxide to form acylpalladium intermediates which reacted with several nucleophiles.[191] Since

10.1002/anie.201502075. f) A. Iglesias, R. Álvarez, Á. R. de Lera, K. Muñiz, *Angew. Chem. Int. Ed.* **2012**, *51*, 2225. g) J. Pan, M. Su, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 8647. For an iridium-catalyzed intermolecular amidation of C(sp^3)–H bonds see: h) T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 4141.

[191] a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318. b) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3327.

then, this field of research has extensively been studied during the last decades for C(sp^2)–H and C(sp)–H ad C–X functionalization.[192] However, just some isolated examples are reported in the literature for the carbonylation of C(sp^3)–H bonds, which highlights again the intrinsic strength of this type of bonds towards its activation. Furthermore, one of the major obstacles in C(sp^3)–H carbonylation is that the excess of CO may inhibit the activation of the bond by competitively occupying coordination sites on the Pd^{II} center, thus preventing the requisite vacant coordination site to enable C–H activation to take place.

The first palladium-catalyzed carbonylation of alkane C(sp^3)–H bonds was reported by Fujiwara in 1989 using $Pd(OAc)_2$, persulfate as oxidant and CF_3COOH as additive under 30 bar atmosphere of CO. In this way carboxylic acids were synthesized with very low yields (Scheme 3.25).[193]



Scheme 3.25

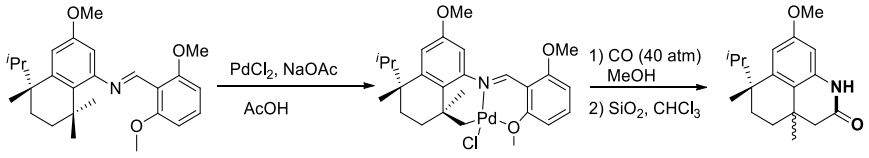
Compared with C(sp^3)–H carbonylation of simple alkanes, selective catalytic carbonylation of a C(sp^3)–H bond in complicated molecules is more challenging and

[192] For selected reviews on carbonylation reactions, see: a) S. T. Gadge, B. M. Bhanage, *RSC Adv.* **2014**, *4*, 10367. b) L. Wu, X. Fang, Q. Liu, R. Jackstell, M. Beller, X. –F. Wu, *ACS Catal.* **2014**, *4*, 2977. c) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114. d) C. F. J. Barnard, *Organometallics*, **2008**, *27*, 5402. e) A. Yamamoto, F. Ozawa, K. Osakada, L. Huang, T. –I. Son, N. Kawasaski, M. –K. Doh, *Pure Appl. Chem.* **1991**, *63*, 687.

[193] a) Y. Fujirawa, K. Takaki, J. Watanabe, Y. Uchida, H. Taniguchi, *Chem. Lett.* **1989**, *18*, 1687. See also: b) K. Satoh, J. Watanabe, K. Takaki, Y. Fujiwara, *Chem. Lett.* **1991**, *20*, 1433. c) K. Nataka, J. Watanabe, K. Takaki, Y. Fujiwara, *Chem. Lett.* **1991**, *20*, 1437.

no relevant studies were reported until the turn of the 21st century.[194,195] In 2010 Yu and co-workers described a general protocol for the Pd^{II}-catalyzed carbonylation of C(sp^3)–H bonds, thereby opening a new entry to 1,4-dicarbonyl compounds (Scheme 3.26).[196] The monodentate and highly acidic amide protecting group [-CONH(4-CF_3-C_6F_4), (Ar_F)] was found to be crucial for the carbonylation of β-C(sp^3)–H bond and cyclization of *N*-arylamides in the presence of 1 atm of CO, AgOAc (2.0 equiv) and TEMPO (2.0 equiv) as oxidants, and KH_2PO_4 (2.0 equiv) as base at 130 ºC for 18 h. The corresponding succinimide derivatives were thus formed in moderate to excellent yields, which could be easily hydrolyzed into the corresponding synthetically useful 1,4-dicarbonyl compounds. The relatively mild reaction conditions tolerated a diverse set of substituents in the substrate, including carboxylic acids containing α-hydrogen atoms, which typically resulted unreactive in other C(sp^3)–H activation reactions thus typically restricting the substrate scope to those containing quaternary α-carbon atoms. Notably, this method was also effective for the carbonylation of methylene C–H bonds in cyclopropanes substrates. Interestingly, cyclopropyl C(sp^3)–H

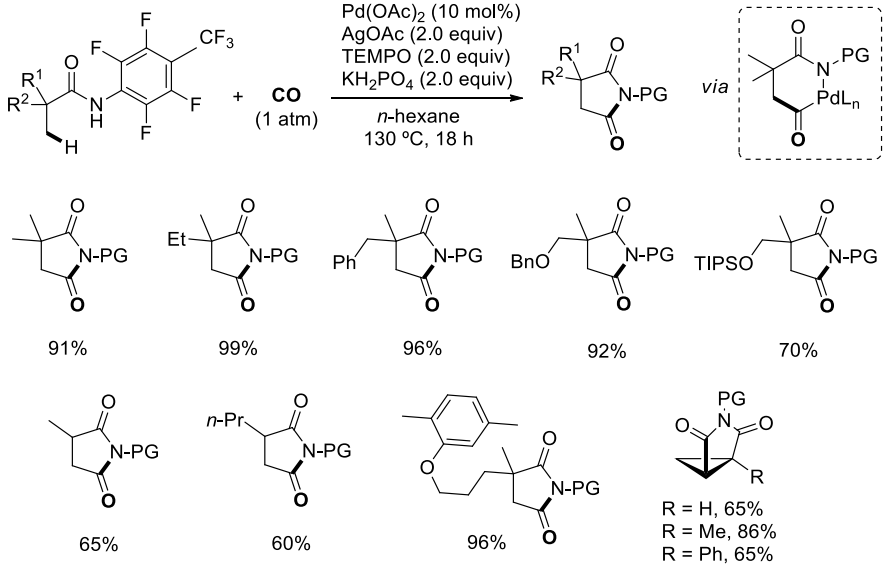
[194] An isolated example of this transformation was presented by Sames in the synthesis of the core of *Teleocidin B4*, where the treatment of a previously preformed palladacycle in the presence of CO yielded the desired aminocarbonylation compound (see Scheme bellow): B. D. Dangel, K. Godula, S. W. Youn, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 11856.



[195] For very recent examples on Pd-catalyzed C(sp^3)–H carbonylation of benzylic and allylic bonds following an electron-transfer mechanism initiated *via* the homolytic cleavage of the peroxide-based oxidant, see: a) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, H. Huang, *J. Am. Chem. Soc.* **2014**, *134*, 9902. b) H. Liu, G. Laurenczy, N. Yan, P. J. Dyson, *Chem. Commun.* **2014**, *50*, 341. c) P. Xie, C. Xia, H. Huang, *Org. Lett.* **2013**, *15*, 3370. d) H. Chen, C. Cai, X. Liu, X. Li, H. Jiang, *Chem. Commun.* **2011**, *47*, 12224.

[196] E. J. Yoo, M. Wasa, J. –Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 17378.

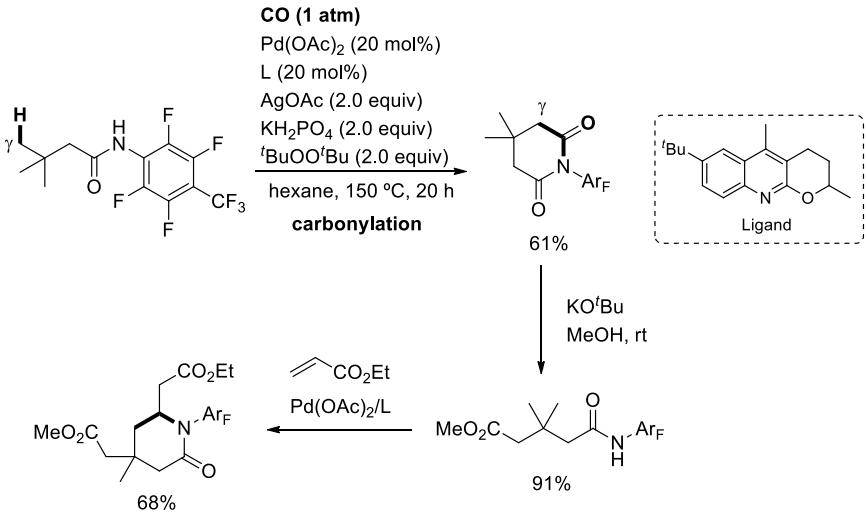
methylene bond could selectively be carbonylated over a methyl C(sp^3)–H bond and an *ortho* aryl C(sp^2)–H bond.



Scheme 3.26

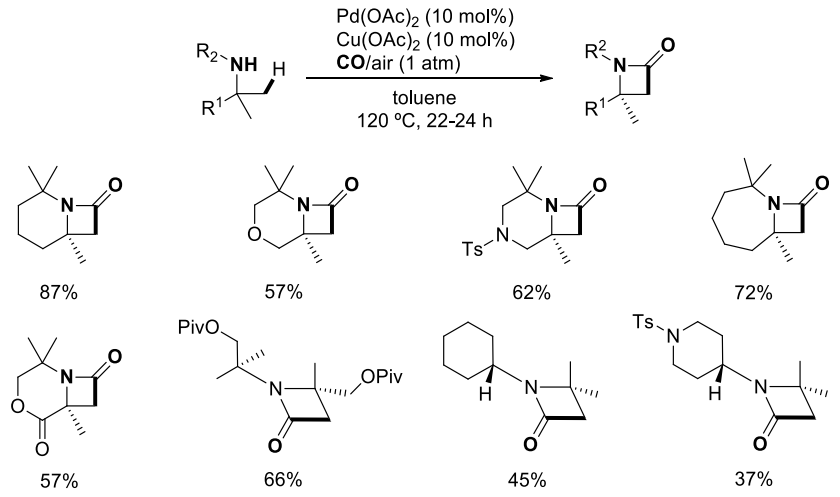
In 2014, based on the combination of the same weakly coordinating amide group with a newly developed quinolone based ligand, a sequential and mono-selective γ-carbonylation/alkenylation procedure for constructing richly functionalized all-carbon β-quaternary centers was developed by Yu and co-workers (Scheme 3.27).[197]

[197] S. Li, G. Chen, C. –G. Feng, W. Gong, J. –Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 5267.



Scheme 3.27

An interesting Pd-catalyzed C(sp^3)–H carbonylation for generating four-membered-ring cyclopalladation was reported by Gaunt and co-workers in 2014.[190a] The four-membered-ring cyclopalladation pathway was found to be operative in systems that do not possess C–H bonds in the positions that would facilitate classical, kinetically more favoured, five-membered-ring cyclopalladates intermediates. In this elegant study, a novel C–H carbonylation reaction for the synthesis of β-lactams was realized *via* activation of a C(sp^3)–H bond belonging to a methyl group adjacent to a secondary amine, thus circumventing possible decomposition pathways, potentially *via* β-hydride elimination. Piperidine, azepine, morpholine, as well as acyclic amine derivatives were found to be effective substrates, producing the resulting β-lactams in good yields. The authors suggested that the C–H palladation step may be reversible under the optimized reaction conditions [$Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (10 mol%), toluene, 120 ºC, 24 h] (Scheme 3.28).



Scheme 3.28

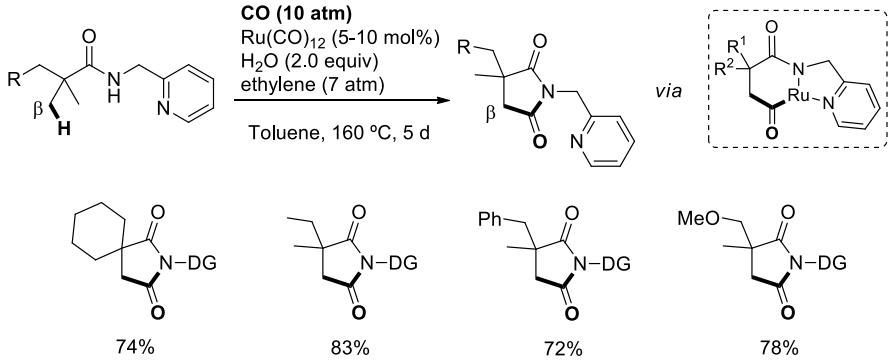
Aside from Pd-catalysis, ruthenium has also proved to be a versatile catalyst for C–H carbonylation reactions, notably thanks to the studies of Murai and Chatani.[198] In 2009, Chatani and co-workers reported a Ru^0-catalyzed aryl C(sp^2)–H carbonylation of amides bearing a 2-aminomethylpyridine as bidentate directing group.[199] The authors reasoned that this bidentate system would bind tightly to the catalyst even under a high CO pressure, thereby permitting the catalyst to come into proximity to a C–H bond. In contrast, a directing group with poor coordinating ability must compete with the high pressure of CO, thus inhibiting the reactivity of the catalyst. Extension of the reaction to the Ru^0-catalyzed carbonylation of β-C(sp^3)–H of aliphatic amides was successful (Scheme 3.29).[200] The ability of the directing group to bind to Ru in the expected *N*,*N*-bidentate fashion was confirmed by X-ray. The regioselective cyclocarbonylation of aliphatic amides with a 2-aminomethylpyridine moiety proceeded smoothly to form the corresponding succinimide products in moderate to

[198] N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, K. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000**, *122*, 12882.

[199] S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 6898.

[200] N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 8070.

good yields in the presence of ethylene and water at 160 ºC for 5 days. The presence of ethylene (7 atm) as hydrogen acceptor and the addition of water to generate an active species were critical for the success of this carbonylation reaction. C–H bonds of methyl groups were found to be preferentially carbonylated.[201]



Scheme 3.29

3.5.1. $Mo(CO)_6$-Mediated palladium-catalyzed carbonylation

Carbonylation catalysis (catalytic insertion of carbon monoxide into organic molecules) occupy a central position in *Organometallic Chemistry* and has experienced a continuous progress, leading to broad applications in the synthesis of a wide variety of simple carbonyl compounds to more complex organic molecules. However, the difficulty in handling toxic, gaseous carbon monoxide, including its storage and transport, represents major disadvantages associated to these methodologies.[202] Unfortunately, such pitfalls reduce the overall utility of carbonylation. Some strategies that address this issue have appeared in the

[201] For a very recent nickel-catalyzed carbonylation example using 8-aminoquinoline as directing group and DMF as CO source, see: X. Wu, Y. Zhao, H. Ge, *J. Am. Chem. Soc.* **2015**, DOI: 10.1021/jacs.5b01671.

[202] a) *Toxicological Profile for Carbon Monoxide*, U. S. Department of Healt and Human Services, Atlanta, Georgia, **2012**. b) P. Carson, C. Mumford, *Hazardous Chemical Hanbook*, Butterworth-Heinemann, Oxford, **2002**.

literature, especially in the last decade, describing carbonylation reactions that can be conducted using substitutes for carbon monoxide, thus avoiding the direct use of gaseous CO. This strategy has been applied in reactions with high utility in organic synthesis such as hydrocarbonylation of alkenes and alkynes, hydroformylation of alkenes, alkoxy-, amino-, and hydrocarbonylation of aromatic and alkenyl halides, and the Pauson-Khand reaction.[203]

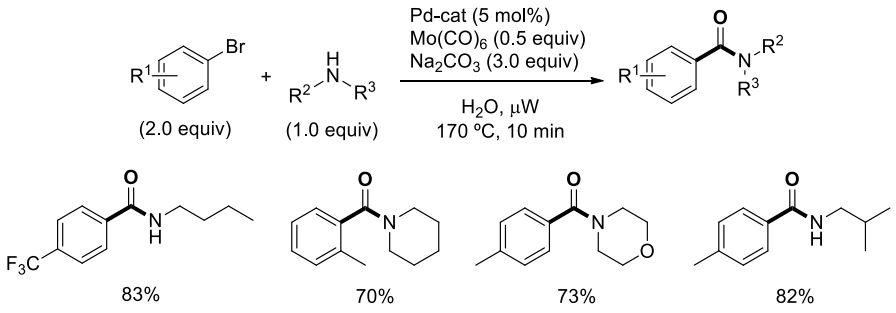
Among the reagents that can be used as substitutes for carbon monoxide, metal carbonyls, which contain carbon monoxide as ligands, such as $Cr(CO)_6$, $W(CO)_6$, $Co_2(CO)_8$ and especially $Mo(CO)_6$, occupy a prominent position. These are solid reagents with the ability of slowly release carbon monoxide *in situ* during the reaction, which represents a distinct advantage over conventional methods relying on carbon monoxide atmosphere in terms of preventing catalyst deactivation by saturation of the metal coordination sites.

The CO-releasing ability of molybdenum hexacarbonyl [$Mo(CO)_6$] in Pd-catalyzed reactions has extensively been demonstrated, mainly by the research group of Larhed.[204] As a representative example, Wu and Larhed described in 2005 a Pd-catalyzed aminocarbonylation reaction of aromatic halides by using solid, easy-to-handle $Mo(CO)_6$ as the only source of carbon monoxide to afford the corresponding secondary and tertiary benzamides under microwave conditions in just 10 min (Scheme 3.30).[205] The reactions were performed in pure water as solvent, in spite of which aminocarbonylation strongly dominated over hydroxycarbonylation.

[203] T. Morimoto, K. Kakiuchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 5580.

[204] For selected publications on $Mo(CO)_6$ CO-releasing in Pd-catalyzed reactions, see: a) N. F. K. Kaiser, A. Hallberg, M. Larhed, *J. Comb. Chem.* **2012**, *4*, 109. b) J. Lindh, A. Fardost, M. Almeida, P. Nilsson, *Tetrahedron Lett.* **2010**, *51*, 2470. c) J. Wannberg, M. Larhed, *J. Org. Chem.* **2005**, *7*, 5750. d) X. Y. Wu, R. Rönn, T. Gossas, M. Lahred, *J. Org. Chem.* **2005**, *70*, 3094. e) X. Y. Wu, P. Nilsson, M. Lahred, *J. Org. Chem.* **2005**, *70*, 346.

[205] X. Y. Wu, M. Larhed, *Org. Lett.* **2005**, *7*, 3327.



Scheme 3.30

3.6. Aim of the project

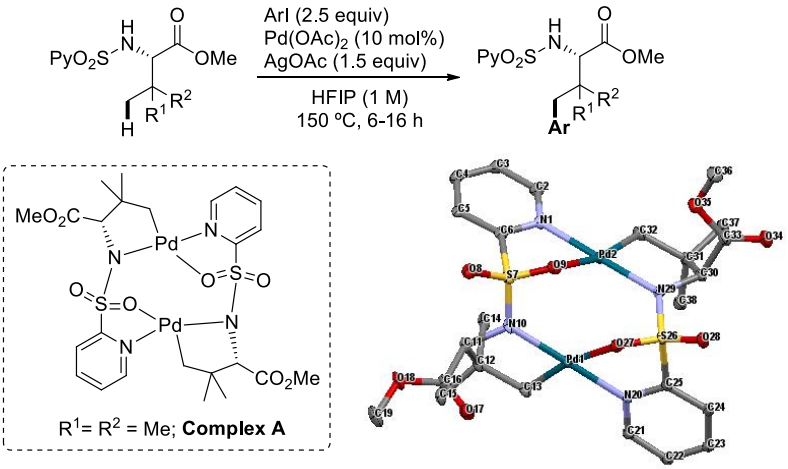
As clearly outlined in this journey by the literature precedents, over the past recent years the field of C(sp^3)–H bond activation/functionalization is receiving increasing attention and has become one of the most active areas of research in organic synthesis, as witnessed by the number of applications in various C–C and C–X bond-forming reactions that have recently arisen. In particular, chelation-assisted direct functionalization (mainly through the use of bidentate directing groups) of α-amino acid derivatives at the aliphatic C–H bonds is receiving growing interest as an emerging tool for the rapid preparation of non-natural amino acids in response to the increasing demand for peptide-based drug discovery programs.

Despite these significant advances, this area of research is still in its infancy and many challenges remain unresolved, thus providing ample opportunities for the development of new and useful C(sp^3)–H functionalization reactions, especially in the synthesis of non-natural α-amino acids. For example, structurally new bidentate directing motifs are needed for overcoming the low reactivity of C(sp^3)–H bonds and improving regioselectivity, which stand as important restrictions that need to be addressed. Indeed, constraints in terms of regioselectivity have hampered the development of efficient methods for the late-stage functionalization of more complex di- and tri-peptides, even though methodologies enabling derivatization of small peptides are highly desirable for the development of peptidomimetics.

On the other hand, the paucity of direct catalytic C–H bond carbonylation protocols described so far contrasts with the plethora of Pd-catalyzed carbonylative transformations of vinylic and aromatic halides available. This scarcity is even much more pronounced in the case of carbonylation of $C(sp^3)$–H bonds, with no single example being applied to α-amino acid derivatives.

Finally, most of the proposed mechanisms are based on preliminary results and lack of solid and thorough experimental and theoretical evidence. Detailed mechanistic studies are necessary for a better understanding of the mechanical aspects ruling these reactions.

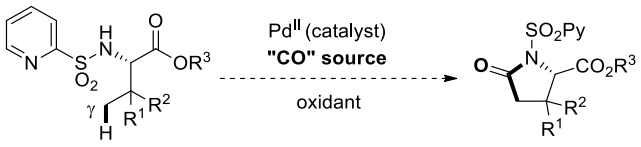
Having laid the fundamental basis in the ability of the *N*-(2-pyridyl)sulfonyl directing group for selective functionalization of aryl and heteroaryl $C(sp^2)$–H bonds,[21-29] our research group next extended this activation concept to the functionalization of $C(sp^3)$–H bonds by developing a Pd-catalyzed arylation on the aliphatic γ-C–H position of readily available *N*-(2-pyridyl)sulfonyl-protected α-amino acid esters with iodoarenes (Scheme 3.31).[32] In our studies, a bimetallic Pd^{II}-complex **A** was isolated (under stoichiometric palladium) and structurally characterized by X-ray, thus highlighting the role as bidentate directing group of the $–SO_2Py$ unit.



Scheme 3.31

On the basis of these precedents and attracted by the above mentioned challenging tasks, ***we envisaged to explore the viability of a novel catalytic γ-C(sp^3)–H carbonylation/cyclization of α-amino acid for the rapid access to highly valuable 5-oxoproline derivatives through a two-fold carbonylation at both the C(γ)–H and N–H bonds*** (Scheme 3.32). A major obstacle for achieving this goal in a catalytic variant is that the excess of CO could inhibit the C–H activation event by competitively occupying coordination sites in the Pd^{II} center. ***A solution to this pitfall might come from the use of $Mo(CO)_6$ (and related species) which enables slow in situ release of CO.***

Furthermore, ***this strategy will be applied to the late-stage functionalization of small peptides (di- and tripeptides)***, which represent a more difficult task because of the potential formation of *N*,*N*- or *N*,*O*-biscoordinated Pd^{II}-complexes. Finally, in addition to exploiting the synthetic potential of this transformation, ***a special focus will be placed on the study of the reaction mechanism, both experimentally and computationally, in order to gain understanding of the factors that control the reactivity and selectivity of catalytic species, which is essential to direct reactivity to novel type of processes.***



Scheme 3.32

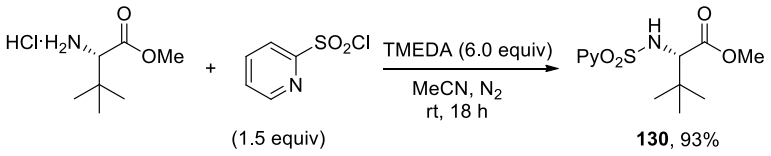
3.7. Results and discussion[206]

3.7.1. Proof of concept: palladium-promoted carbonylation of complex A

In our previous studies on the Pd-catalyzed γ-arylation of amino acid derivatives directed by the *N*-(2-pyridyl)sulfonyl group, a bimetallic palladium(II) γ-cyclometallated **complex A**, derived from *N*-(2-pyridyl)sulfonyl-protected *tert*-leucine, was isolated and characterized structurally by X-ray diffraction analysis.[32] We envisioned that this preformed Pd^{II}-complex could provide and ideal platform to expand our design approach to other useful C–H functionalization reactions involving C–C and C–X bond formation. In particular, we focused on testing whether or not carbon monoxide insertion would be an amenable transformation.

- ***Synthesis of complex A***

N-(2-pyridyl)sulfonyl *tert*-leucine derivative **130** was readily prepared by treating *tert*-leucine methyl ester hydrochloride (1.0 equiv) with (2-pyridyl)sulfonyl chloride (1.5 equiv) using TMEDA (6.0 equiv) as base in acetonitrile at rt for 18 h. The corresponding sulfonamide was obtained in good yield (93%) as a bench-stable solid.

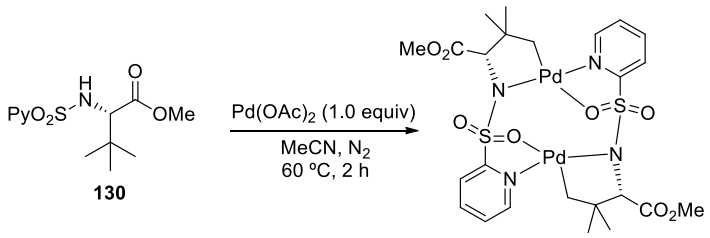


Scheme 3.33

When this *N*-SO_2Py-protected *tert*-leucine derivative **130** was treated with stoichiometric amount of palladium(II) acetate (1.0 equiv) in anhydrous acetonitrile at 60 ºC for 2 h, we observed the clean formation of the bimetallic palladium(II) **complex A**, which was isolated in 91% yield as an air-stable orange solid (Scheme 3.34). This complex was crystallized in a DCM/pentane mixture, proving to be, by

[206] This research Project was also supervised by Dr. Nuria Rodríguez.

X-ray diffraction analysis, a bimetallic five-membered ring palladacycle, metallated at one carbon of the methyl *tert*-leucine groups. Interestingly, in this dimeric complex the slightly distorted square planar Pd^{II} atom is bonded to the sulfonamide nitrogen and the γ-palladated carbon, while the other two coordination positions are occupied by the pyridine nitrogen and one of the sulfonylic oxygens.[207]



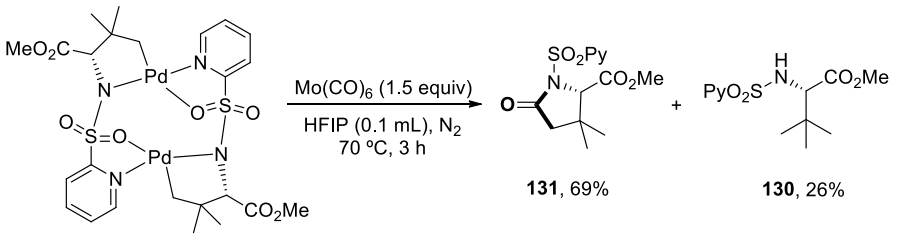
Scheme 3.34

- ***Stoichiometric carbonylation of complex A***

In our initial attempt, the reaction of **complex A** with $Mo(CO)_6$ (1.5 equiv) using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)[208] as solvent at 70 ºC for 3 h, resulted in the clean formation of the expected γ-lactam **131**, which was isolated in 69% yield, along with a significant amount of decomplexated *tert*-leucine derivative **130** (26%) (Scheme 3.35).

[207] The Pd(1)-Pd(2) distance is 3.1276 (12) Å, which is, within the sum of van der Waals radii (3.26 Å), and the Pd–C distance [1.997 (11) Å] are similar to the distances found in five-membered ring metallated complexes. For reported Pd–Pd and Pd–C distances in related complexes, see: a) A. Bondi, *J. Phys, Chem.* **1964**, *68*, 441. See also: b) J. Dupont, M. Pfeffer, *Palladacycles*, Wiley-VCH, Weinheim, **2008**.

[208] The choice of HFIP as solvent proved to be essential to realizing our previously developed γ-C(sp^3)–H arylation of α-amino acid derivatives (see reference 32).



Complex A (0.013 mmol)

Scheme 3.35

Monitoring this stoichiometric reaction by ^{1}H NMR in CD_3CN as solvent (much less expensive than deuterated-HFIP) at rt in the presence of 0.33 equiv of $Mo(CO)_6$, led us to find a fast and clean formation of an unstable **intermediate B** which reached its highest concentration after 2.5 h of reaction (roughly **complex A/intermediate B** ratio = 1:1), as shown in Figure 3.1. The resulting mixture remained almost unaltered for a period of further 2.0-2.5 h and suddenly, a relatively fast conversion of **intermediate B** into the final γ-lactam **131** was observed, with a complete disappearance of characteristics signals of **intermediate B** upon 7.5 h. A 60% conversion towards **131** was attained after 9.5 h of reaction. Nevertheless, full conversion of **complex A** into γ-lactam **131** was achieved under extended reaction times (24 h). Figure 3.2 shows the complete reaction kinetic profile from a measure of conversion (%) *versus* time (hours).

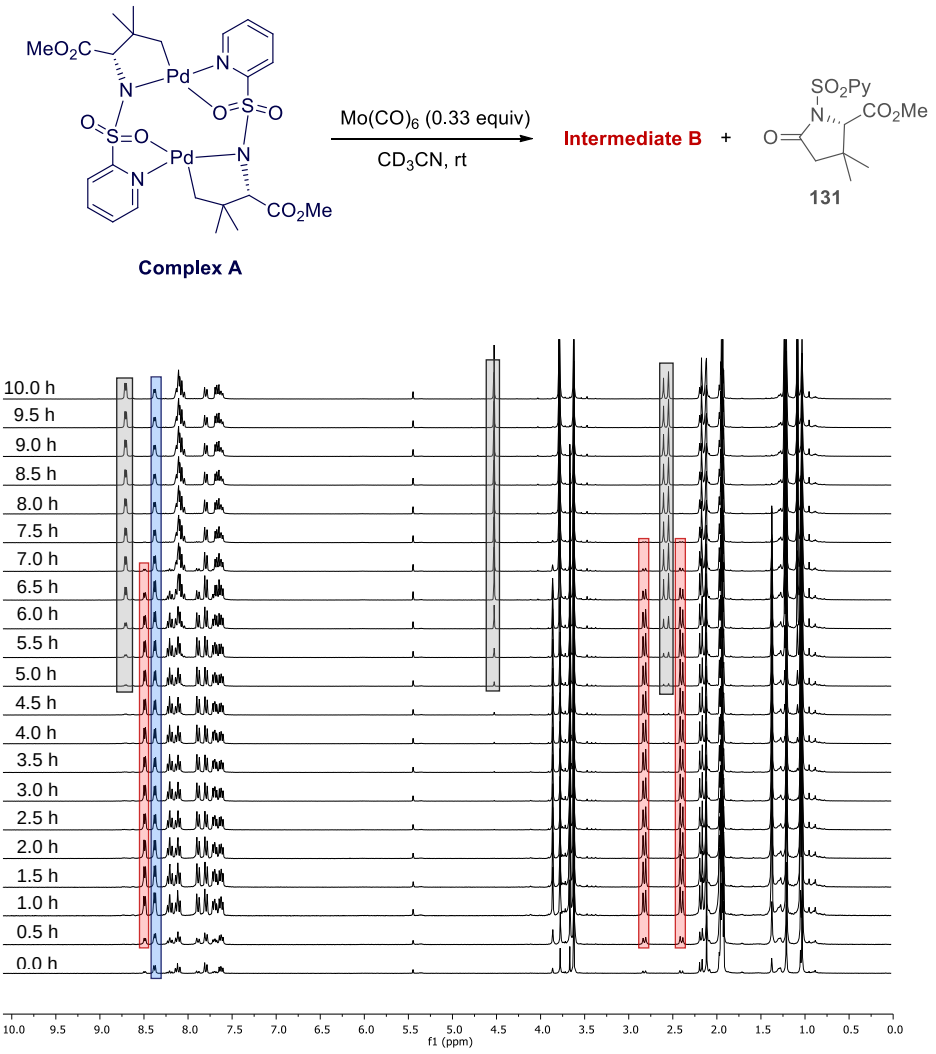

MeO2C
Pd
N
O
S
O
Pd
N
CO2Me
Complex A
Mo(CO)6 (0.33 equiv)
CD3CN, rt
Intermediate B
+
SO2Py
N
CO2Me
O
131
10.0 h
9.5 h
9.0 h
8.5 h
8.0 h
7.5 h
7.0 h
6.5 h
6.0 h
5.5 h
5.0 h
4.5 h
4.0 h
3.5 h
3.0 h
2.5 h
2.0 h
1.5 h
1.0 h
0.5 h
0.0 h
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

Figure 3.1

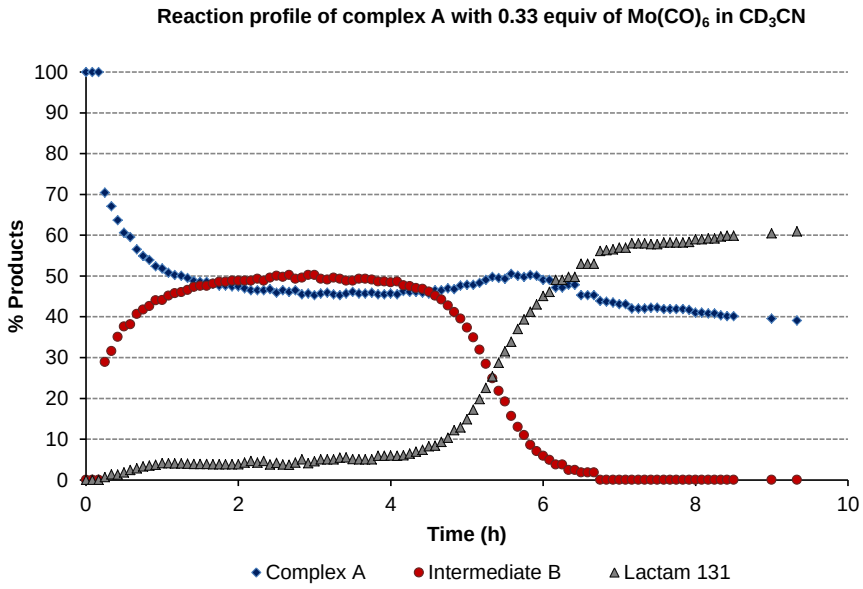


Figure 3.2

To evaluate the effect of the amount of $Mo(CO)_6$ present in the reaction, we undertook a similar kinetic profile in the presence of twice the amount of $Mo(CO)_6$ (0.66 equiv) under otherwise identical reaction conditions. The results are displayed in Figure 3.3. As in the former case, **intermediate B** was quickly formed, reaching a higher conversion (75%) after 2.5 h. However, under these conditions **intermediate B** showed increased stability, remaining unaltered in the mixture for a longer period of time (about 6 h) before it slowly starts to decompose forming γ-lactam **131** after 8 h of reaction. Indeed, upon 9.5 h of reaction time, the expected product **131** was formed in only 20% of conversion yield, whereas a 60% of **intermediate B** still remained in the mixture along with a 20% of the starting **complex A**. Notably, however, as previously observed when using 0.33 equiv of $Mo(CO)_6$, increasing the reaction time to 24 h resulted in a complete conversion of **complex A** into the γ-lactam **131** (determined by ^{1}H MNR).

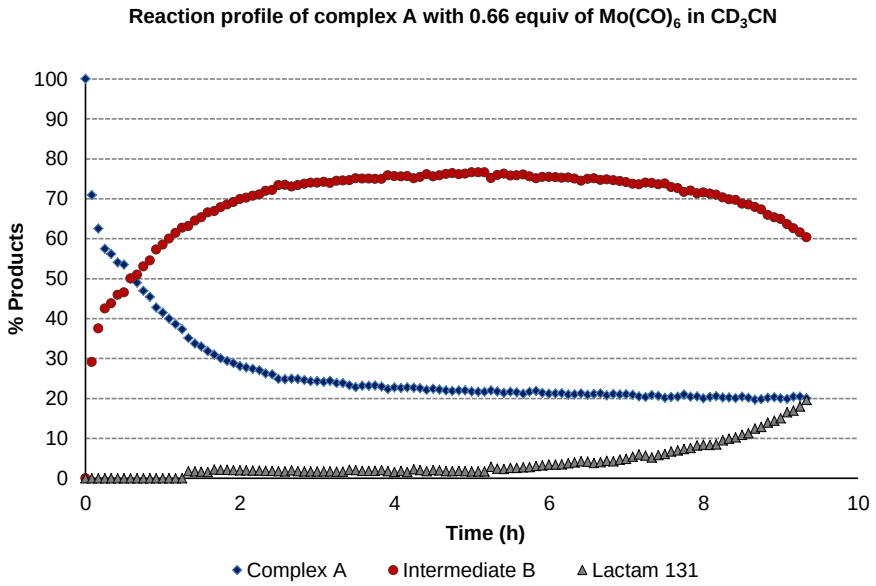
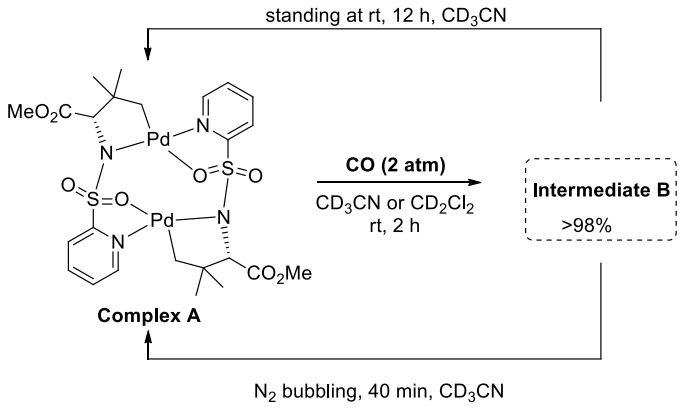


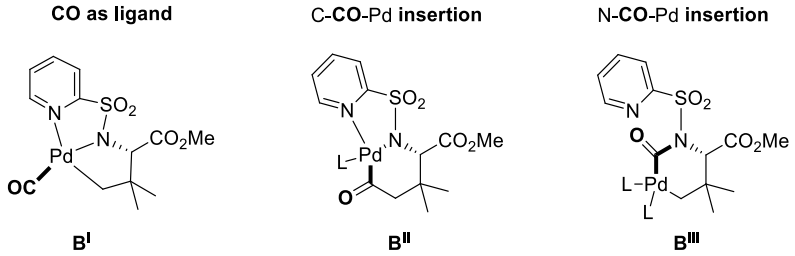
Figure 3.3

This different reaction outcome suggested that both the rate of formation of **intermediate B** and its lifetime, strongly depended on the concentration of carbon monoxide present in the reaction mixture (the higher the amount of CO, the faster formation and increased stability of **intermediate B**). In line with this observation, when the preformed palladium **complex A** was stirred in CD_3CN or CD_2Cl_2 under gaseous CO (2 atm), a clean and complete conversion of **complex A** into the **intermediate B** was observed in just 2 h at rt. Upon standing for 12 h in CD_3CN in the absence of a CO atmosphere, **intermediate B** slowly evolves towards **complex A**. Interestingly, the conversion of **intermediate B** into **complex A** was found to be strongly accelerated by bubbling N_2 into the CD_3CN reaction mixture to displace the dissolved CO gas present (Scheme 3.36).



Scheme 3.36

At this point we speculated that the **intermediate B** could be either a palladium-carbonyl complex preceding carbonyl insertion (species **B**^{I}) or a palladium complex resulting from 1,1-migratory insertion of CO into the Pd–C or the Pd–N bond (species **B**^{II} or **B**^{III}, respectively, Scheme 3.37). Nevertheless, a detailed structural characterization study of this intermediate is provided at the end of this Chapter along with some mechanistic insights.

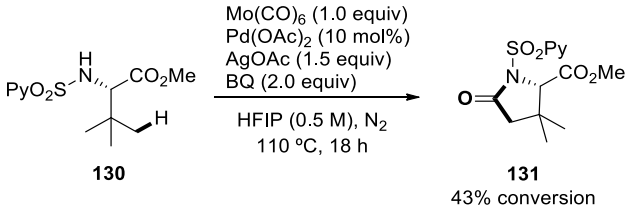


Scheme 3.37

While these results provided a proof-of-concept, we next embarked on the challenging task of developing a catalytic, rather than stoichiometric, version of this carbonylation reaction.

3.7.2. Pd-catalyzed γ-C(sp^3)–H carbonylation of *N*-(2-pyridyl)sulfonyl-protected α-amino esters

On the basis of literature precedents on Pd-catalyzed C(sp^3)–H arylation of simple carboxylic acids[209] and the knowledge acquired in our previously reported study on the Pd-catalyzed *N*-SO_2Py-protected C(sp^3)–H arylation of amino acid derivatives,[32] we started our investigations by subjecting the *tert*-leucine derivative **130** to carbonylation with $Mo(CO)_6$ (1.0 equiv) in the presence of a catalytic amount of $Pd(OAc)_2$ (10 mol%) and stoichiometric amount of AgOAc (1.5 equiv) and 1,4-benzoquinone (BQ, 2.0 equiv)[210] as oxidants in HFIP (0.5 M) at 110 ºC for 18 h. Under these reaction conditions, an encouraging 43% conversion towards the expected γ-lactam **131** was observed, being the only detected reaction product (along with the remaining 57% of unreacted **130**) by ^{1}H NMR in the crude mixture (Scheme 3.38). This promising outcome sparked our interest to optimize the reaction conditions in an attempt to improve the efficiency of this carbonylation reaction. Hence, a careful evaluation of some structural and reaction parameters was next performed.



130 **131**
43% conversion

Scheme 3.38

[209] R. Giri, N. Maugel, J. –J. Li, D. –H. Wang, S. P. Brezzano, L. B. Saunders, J. –Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510.

[210] For mechanistic studies on the key role of BQ in Pd-catalyzed oxidative cross-coupling reactions, see: a) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 9651. For the use of benzoquinone as oxidant in C–H functionalization reactions, see: b) F. Meyer, C. Limberg, *Organometallic Oxidation Catalysis*, *Top. Organomet. Chem.*, Springer, Berlin Heidelberg, **2007**.

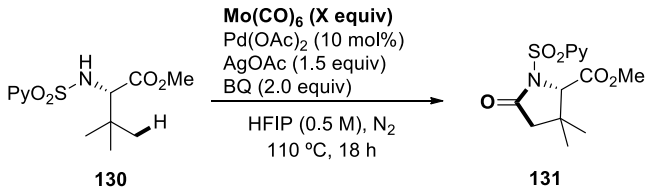
- ***Study of the amount of $Mo(CO)_6$***

Having observed in the previous stoichiometric studies that the amount of $Mo(CO)_6$ (directly related to the concentration of CO present in the reaction media) strongly influenced the kinetic of the formation of the carbonylation product, we speculated that an excess of CO released from $Mo(CO)_6$ could deactivate the catalytic Pd active species, thereby leading to a poor conversion. Therefore, we reasoned that lowering the amount of $Mo(CO)_6$ would be beneficial to the reaction. To confirm our proposition, a detailed study of the dependency of reaction efficiency upon the amount of $Mo(CO)_6$ was carried out. As shown in Table 3.1, the reaction was found to be strongly affected by the amount of $Mo(CO)_6$.

In accordance with our hypothesis, lowering the amount of $Mo(CO)_6$ positively influenced the reaction outcome, guiding us to a substantial and consistent increase in conversion when decreasing the number of equivalents of $Mo(CO)_6$ from 1.0 (43% conversion, entry 1) to 0.5 (67% conversion, entry 2) and 0.33 (90% conversion, entry 3).[211] However, further decrease of the amount of $Mo(CO)_6$ hold a negative impact, with 53% conversion being observed with 0.20 equiv (entry 4). Not unexpectedly, an attenuation of the catalytic activity was consistently observed by increasing the amount of $Mo(CO)_6$ over 1.0 equiv (entries 5 and 6), thus providing additional weigh to the idea that an excess of CO in the reaction medium exerts a negative role on the catalytic activity. Finally, as expected, a control experiment omitting $Mo(CO)_6$ determined that γ-lactam **131** is not produced, thus confirming that this reagent acts as the source of CO (entry 7).

[211] This result indicates that 1.0 equiv of CO corresponds to 3 units of L in $Mo(CO)_6$.

Table 3.1: Study of the amount of $Mo(CO)_6$

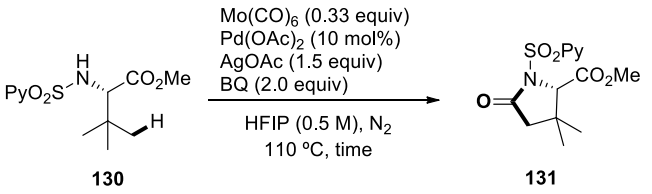


130 **131**

Entry	$Mo(CO)_6$ (equiv)	**131** Yield (%)[a]
1	1.00	43
2	0.50	67
3	0.33	90 / 83[b]
4	0.20	53
5	2.00	42
6	4.00	36
7	0	0

[a] Conversion yields by ^{1}H NMR spectroscopy; [b] Isolated yield.

Importantly, simply adjusting the amount of $Mo(CO)_6$ to 0.33 equiv led us to find conditions for the efficient transformation of *tert*-leucine derivative **130** into the pyroglutamic acid derivative **131**, which could be isolated in 83% yield after purification by column chromatography. Furthermore, we successfully performed an experiment on a larger gram-scale to demonstrate the practicality of this methodology which afforded product **131** in 77% isolated yield after an extended reaction time of 24 h (Scheme 3.39).



130 **131**

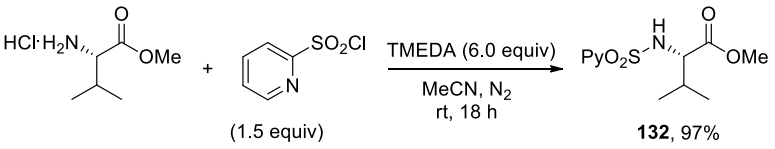
mmol	time (h)	% isolated yied
0.10	18	83
3.50 (***1.0 gram***)	24	77

Scheme 3.39

- ***Carbonylation of L-valine derivative 132***

At this juncture, our attention was shifted to the carbonylation of the corresponding valine derivative **132**. There are several reasons behind using **132** as starting material for the next optimization studies. First, this substrate would test whether the presence of a *tert*-butyl group is required for the C–H carbonylation event or the kinetically less favourable *iso*-propyl group is also amenable to this transformation. Second, because the *iso*-propyl unit contains two diastereotopic methyl groups, this substrate would test the diastereoselectivity of the carbonylation process. Third, since *L*-valine is a natural α-amino acid, its enantiomerically pure derivatives can be purchased from commercial sources at a much cheaper price than the *tert*-leucine analogue, thus facilitating the examination of whether or not its stereochemical integrity is preserved under the reaction conditions.

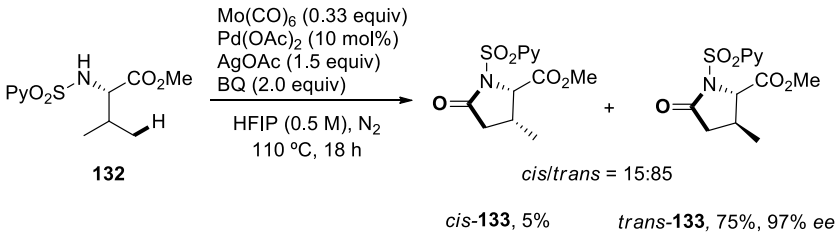
N-(2-pyridyl)sulfonyl *L*-valine derivative **132** was synthesized in excellent yield (97%) from the commercially available *L*-valine methyl ester hydrochloride by reaction with (2-pyridyl)sulfonyl chloride under the typical *N*-sulfonylation conditions (Scheme 3.38).



Scheme 3.38

L-Valine-*N*-(2-pyridyl)sulfonyl derivative **132** was next subjected to C–H carbonylation reaction under our previously optimized reaction conditions [$Mo(CO)_6$ (0.33 equiv), $Pd(OAc)_2$ (10 mol%), BQ (2.0 equiv), AgOAc (1.5 equiv), HFIP as solvent (0.5 M), at 110 ºC for 18 h]. Delightfully, the reaction with this derivative proceeded smoothly to afford the expected amidocarbonylation product **133** as a 15:85 mixture of *cis*/*trans* diastereoisomers. This good *anti*-diastereoselectivity is remarkable, revealing a marked preference for C–H activation of the pro-*S* methyl group of the *L*-valine derivative **132**.[212] Additionally, the resulting diastereoisomeric mixture of *cis*-**133** and *trans*-**133** could be easily separated by conventional chromatography, upon which the major component was isolated diastereomerically pure in 75% yield, while the minor *cis*-diastereoisomer was obtained in 5% yield (Scheme 3.41). Importantly, it was found that the Pd-catalyzed event takes place preserving the stereochemical integrity at the α-position, as demonstrated by the very high enantiomeric purity of product *trans*-**133** (determined to be 97% *ee* by HPLC using a chiral stationary phase).

[212] This *trans*-preference is in agreement with the diastereoselectivity previously observed in our research group in the Pd-catalyzed γ-mono-arylation of **132** (see reference 32).



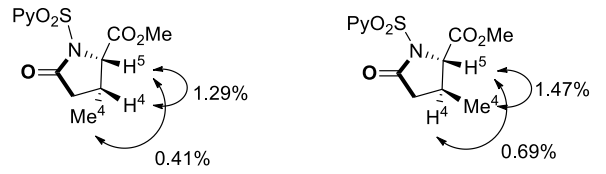
132

cis/*trans* = 15:85

cis-**133**, 5% *trans*-**133**, 75%, 97% *ee*

Scheme 3.41

The *cis*/*trans* ratio was determined by ^{1}H NMR from the reaction mixture and the identity of both diastereoisomers could be unambiguously stablished by NMR experiments, mainly by the coupling constants of H^5 [*cis*-**133**; 4.99 ppm (d, *J* = 8.5 Hz) and *trans*-**133**; 4.60 ppm (d, *J* = 3.0 Hz)] and the NOE correlation experiments as depicted in Figure 3.4. When H^5 was selectively irradiated, a significant NOE correlation with the methyl group (Me^4) was observed in the case of *trans*-**133** (1.47%), while a much weaker correlation of 0.41% was observed for *cis*-**133**. Additionally, the NOE correlation between of H^4-H^5 in *trans*-**133** derivative, presented a value of 0.69% while in *cis*-**133** an increased value of 1.29% was determined for the same H^4-H^5 correlation, indicating that both H^4 and H^5 are oriented towards the same face of the molecule.



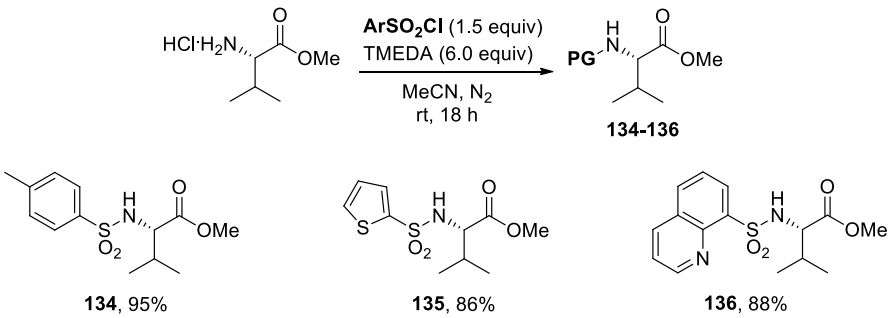
H^5: 4.99 ppm (d, *J* = 8.5 Hz) *cis*-**133**

H^5: 4.60 ppm (d, *J* = 3.0 Hz) *trans*-**133**

Figure 3.4

➢ ***Evaluation of the effect of the directing/protecting group***

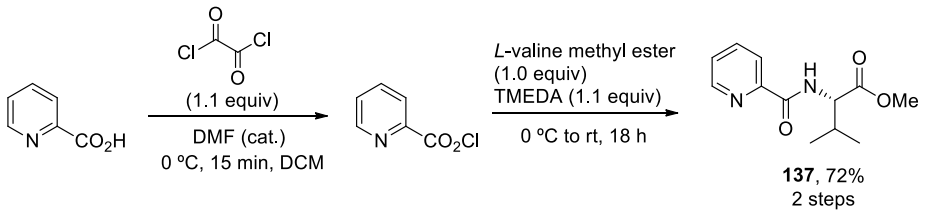
Although the structure of the bimetallic complex of γ-cyclopalladation of *tert*-leucine derivative **130** (**complex A**) strongly suggested that the NH-(SO_2Py) directing group would be uniquely effective for this transformation, we were interested in confirming this issue by screening other potentially coordination *N*-protecting groups. We therefore synthesized a set of differently *N*-protected-*L*-valine derivatives presenting various aryl and heteroaryl sulfonyl groups, **134-136**, in good to excellent yields (86-95%), from the corresponding sulfonyl chloride, following the typical *N*-sulfonylation protocol (Scheme 3.42).



Scheme 3.42

Likewise, it was also very interesting to investigate the role of the sulfonyl group (not only the 2-pyridyl unit) in the efficiency of the reaction. For that purpose, the *N*-(2-pyridyl)carbonyl-*L*-valine derivative **137**, also containing the electronically deactivated 2-pyridyl coordinating unit but connected to the substrate by a carbonyl group instead of a sulfonyl group, was also prepared following a previously described protocol.[213] Activation of 2-picolinic acid with oxalyl chloride and treatment of the resulting acid chloride with *L*-valine methyl ester hydrochloride in the presence of TMEDA as base (1.1 equiv) led to the formation of the expected product **137** in good yield (72%, Scheme 3.43).

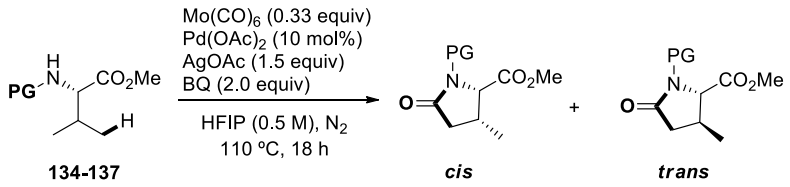
[213] M. D. Markey, Y. Fu, T. R. Kelly, *Org. Lett*. **2007**, *9*, 3255.



Scheme 3.43

This set of *L*-valine derivatives (**134-137**), along with *L*-valine methyl ester hydrochloride itself, was next examined in the carbonylation reaction under the optimized conditions and the results are summarized in Table 3.2. While *L*-valine methyl ester hydrochloride decomposed under the reaction conditions (entry 1), the NH-Ts derivative **134** and the NH-(2-thienyl)sulfonyl derivative **135** were recovered unaltered without detecting any carbonylation product (entries 3 and 4, respectively). The reaction of the (8-quinolyl)sulfonyl and (2-pyridyl)carbonyl derivatives (**136** and **137**, respectively) delivered a complex mixture of products in low conversion (< 15%) (entries 5 and 6) even though in the case of **137** characteristic signals corresponding to the expected lactam product could be detected by ^{1}H NMR in the crude reaction mixture. Interestingly, the lack of reaction efficiency observed for the (2-pyridyl)carbonyl-protected substrate **137** emphasizes the cooperative directing role of both the sulfonyl and the 2-pyridyl moieties in the C–H activation process.

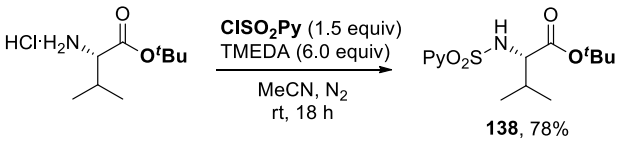
Table 3.2: Evaluation of the effect of the directing/protecting group



Entry	PG	Yield (%)[a]	*cis*/*trans* ratio[b]
1	NH_2.HCl[c]	-[d]	-
2	(2-pyridyl)SO_2- **132**	87 / 80[e]	15:85
3	TolSO_2 **134**	-[f]	-
4	(2-thienyl)SO_2- **135**	-[f]	-
5	(8-quinolyl)SO_2-**136**	< 15	-
6	(2-pyridyl)CO- **137**	< 15	-

[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *cis*/*trans* ratio determined by ^{1}H NMR spectroscopy from the crude mixture; [c] 1.0 equiv of Et_3N was added; [d] Decomposition; [e] Isolated yield, *cis*-**133** (5%) and *trans*-**133** (75%); [f] No reaction.

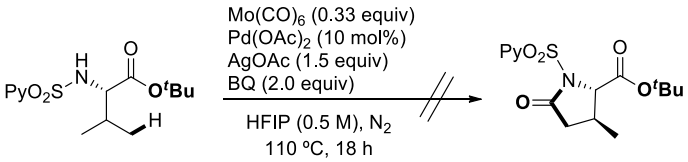
We also reasoned that variations of the steric nature of the ester substituent in **132** from a methyl group to a bulkier *tert*-butyl group could be beneficial to the diastereoselectivity of the reaction. To test this possibility, the *N*-(2-pyridyl)sulfonyl derivative **138** was prepared from the commercially available *L*-valine *tert*-butyl ester hydrochloride in good yield (78%) following the standard *N*-protection procedure (Scheme 3.44).



138, 78%

Scheme 3.44

However, the *tert*-butyl ester derivative **138** suffered from reduced stability when subjected to the standard carbonylation conditions and only by-products derived from decomposition were observed by ^{1}H NMR. This failure is likely due to the increased lability of the *tert*-butyl ester moiety under prolonged heating conditions.



138

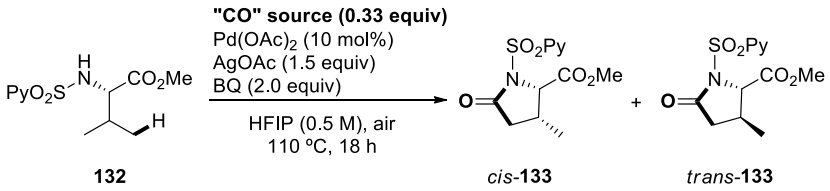
Scheme 3.45

- ***Evaluation of the carbonyl source***

Having demonstrated the unique ability of the (2-pyridyl)sulfonyl as directing group in this C–H activation/carbonylative cyclization reaction, we next focused on exploring alternative carbon monoxide sources that could enhance the reactivity. The results are summarized in Table 3.3. A screen of metal carbonyl complexes different from $Mo(CO)_6$ typically used as carbon monoxide sources[203,204] led to poorer reaction efficiency. For example, the use of $Cr(CO)_6$ also provided the γ-lactam product **133**, but in a much lower yield (19%) and negligible *trans*-diastereoselectivity (*cis*/*trans* = 48:52, entry 2). The carbonyl cobalt(0) complex $Co_2(CO)_8$ was even less effective, providing only traces of the expected product **133** (about 5% conversion, entry 3). After these discouraging results, we also tested the effect of gaseous carbon monoxide. When the reaction of **132** was carried out under CO atmosphere (1 atm,

sealed tube), the expected prolinone **133** was obtained in 41% yield with virtually no diastereoselectivity (*cis*/*trans* = 48:52, entry 4). This lower efficiency under CO atmosphere is in line with our previous observation that an increase of the amount of $Mo(CO)_6$ in the reaction medium was detrimental for the reaction outcome, likely due to catalyst deactivation under excess of carbon monoxide. However, the reasons behind the loss of diastereoselectivity upon changing the $Mo(CO)_6$ to other sources of carbon monoxide are not clear at the present time. Nevertheless, this study evidenced the unique effectiveness of the $Mo(CO)_6$ as carbonylation reagent for this transformation in terms of both reactivity and *trans*-diastereoselectivity.

Table 3.3: Evaluation of the carbonyl source



132 *cis*-**133** *trans*-**133**

Entry	"CO" source	**133** Yield (%)[a]	*cis*/*trans* [b]
1	$Mo(CO)_6$	87	15:85
2	$Cr(CO)_6$	19	48:52
3	$Co_2(CO)_8$	<5	-
4	CO (1.0 atm)	41	48:52

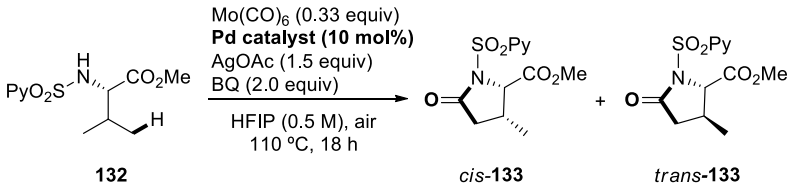
[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *cis*/*trans* ratio determined by ^{1}H NMR spectroscopy from the crude mixture.

- ***Evaluation of the palladium catalyst***

We continued our optimization studies by evaluating the effect of different palladium salts on the reactivity and diastereoselectivity in the model carbonylative cyclization of **132** (Table 3.4). As expected, the control experiment in the absence of any palladium catalyst resulted in no reaction (entry 1). A screen of a number of

different Pd^{II} complexes revealed their ability to promote the carbonylation reaction, but failed in providing a beneficial impact compared to the results obtained earlier with $Pd(OAc)_2$ (entries 3-7). In all cases, lower conversion (39-60%) and lower diastereoselectivity (consistently close to the *cis*/*trans* = 30:70 level) were attained. The attempted use of palladium(0) species, such as $Pd(PPh_3)_4$ or $Pd(dba)_2$ also proved to be futile, with no significant differences observed (entries 8 and 9, respectively).

Table 3.4: Evaluation of the palladium catalyst



132 *cis*-**133** *trans*-**133**

Entry	Pd source	**133** Yield (%)[a]	*cis*/*trans* ratio[b]
1	-	-[c]	-
2	$Pd(OAc)_2$	87	15:85
3	$Pd(TFA)_2$	57	23:77
4	$Pd(acac)_2$	60	27:73
5	$PdCl_2(MeCN)_2$	40	30:70
6	$PdCl_2(PPh_3)_2$	41	27:73
7	$Pd(BF_4)_2(MeCN)_4$	39	26:74
8	$Pd(PPh_3)_4$	33	30:70
9	$Pd(dba)_2$	55	28:72

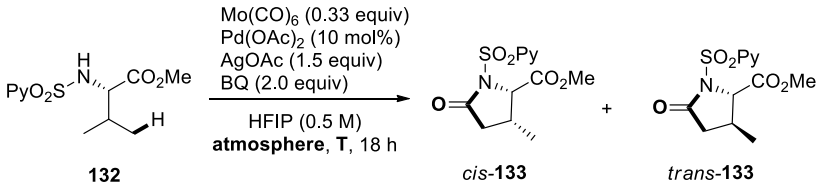
[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *cis*/*trans* ratio determined by ^{1}H NMR spectroscopy from the crude mixture; [c] No reaction.

- ***Evaluation of the effect of the temperature and aerobic/anaerobic conditions***

We next carried out a set of experiments in order to evaluate the influence of the temperature and the effect of aerobic/anaerobic conditions (Table 3.5). The reaction proceeded smoothly under air atmosphere, providing similar results to those ones obtained under inert atmosphere (86% yield, *cis*/*trans* = 16:84, entry 2). In sharp contrast, bubbling molecular oxygen resulted in negligible conversion towards the expected γ-lactam **133** (entry 3).

On the other hand, a detrimental effect in the reactivity was observed when the temperature was decreased to 70 ºC, indicating that the C–H activation process might not occur at lower temperatures (4% yield, entry 4). When the temperature was increased to 140 ºC, both the conversion and the diastereoisomeric ratio were slightly lower in comparison with the results obtained at 110 ºC. This lower conversion is probably due to competitive catalyst decomposition under harsher reaction conditions (66% yield, *cis*/*trans* = 21:79, entry 5).

Table 3.5: Evaluation of the effect of the temperature and aerobic/anaerobic conditions



132 *cis*-**133** *trans*-**133**

Entry	Conditions	**133** Yield (%)[a]	*cis*/*trans* ratio[b]
1	N_2/110 ºC	87 / 80[c]	15:85
2	air/110 ºC	86	16:84
3	O_2/110 ºC	-[d]	-
4	air/70 ºC	4	-
5	air/140 ºC	66	21:79

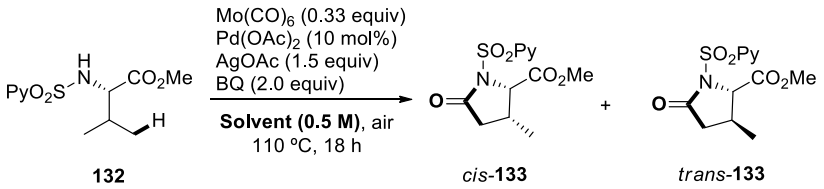
[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *cis*/*trans* ratio determined by ^{1}H NMR spectroscopy from the crude mixture; [c] Isolated yield, *cis*-**133** (5%) and *trans*-**133** (75%); [d] No reaction.

- ***Evaluation of the solvent and the concentration***

A brief study of the solvent and the concentration was subsequently performed in the model reaction of *L*-valine derivative **132** (Table 3.6). Other polar protic solvents such as CF_3CO_2H and ^{t}Amyl-OH completely inhibited the reaction, resulting in the exclusive recovery of the starting material unaltered with no sign of carbonylation product, as determined by ^{1}H NMR analysis of the crude reaction mixture (entries 2 and 3, respectively). Changing to aprotic polar solvents such as DMF, DMSO, NMP or MeCN resulted in no reactivity or a very poor conversion towards the expected cyclized product **133** (0-13% yield, entries 4-7). A lower diastereoisomeric ratio was observed in those cases in which the conversion was high enough to measure accurately the ratio of diastereoisomers (*cis*/*trans* = 30:70-25:75). The use of DCE, a

less polar aprotic solvent which is widely used in C–H activation processes, proved to be also incompatible with our catalytic system, providing just a 17% of conversion towards **133**, although with an acceptable diastereoselectivity (*cis*/*trans* = 20:80, entry 8).

Table 3.6: Evaluation of the solvent

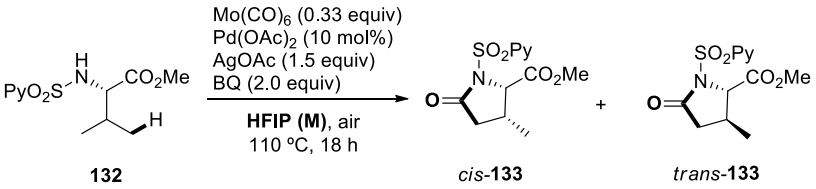


Entry	Solvent (0.5 M)	**133** Yield (%)[a]	*cis*/*trans* ratio[b]
1	HFIP	86	16:84
2	CF_3CO_2H	-[c]	-
3	^{t}Amyl-OH	-[c]	-
4	DMF	13	25:75
5	DMSO	-[c]	-
6	NMP	8	-
7	MeCN	9	30:70
8	DCE	17	20:80

[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *cis*/*trans* ratio determined by ^{1}H NMR spectroscopy from the crude mixture; [c] No reaction.

Variation of the concentration of the reaction medium appeared to have little impact on reactivity. However, unexpectedly, this reaction parameter strongly influenced the diastereoselectivity of the reaction. Thus, whereas doubling the concentration of the reaction from 0.5 M to 1.0 M resulted in similar conversion yield (83%) and slightly improved *trans*-diastereoselectivity (*cis*/*trans* = 13:87), a 5-fold decrease in concentration (from 0.5 M to 0.1 M) delivered the product **133** in high

conversion (80%) but almost no diastereoselectivity (*cis*/*trans* = 46:54). At the present stage of development, we have no clear explanation for this effect.



132 *cis*-**133** *trans*-**133**

concentration	conversion	*cis*/*trans* ratio
0.1 M	80	46:54
0.5 M	86	16:84
1.0 M	83	13:87

Scheme 3.44

- ***Evaluation of the oxidant combination***

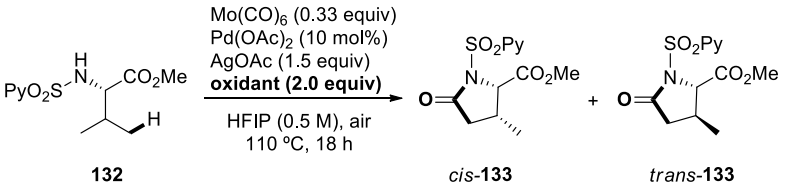
In C–H functionalization processes, the oxidant generally plays a key role in the reaction success. Therefore, we decided to see how important was the role of our oxidant combination (1,4-benzoquinone + AgOAc) in determining the catalytic activity.

- *Evaluation of the role of 1,4-benzoquinone (BQ)*[210]

Some oxidants, such as benzoquinone derivatives, not only oxidize the palladium(0) at the end of the catalytic cycle, but also they can act as potential ligands of the intermediate palladium active species. The evaluation of the role of 1,4-benzoquinone component in the model carbonylation reaction of **132** is presented in Table 3.7. In the absence of BQ just a 15% conversion towards **133** was detected, thus highlighting the crucial role of this additive in our catalyst system (entry 1). The use of bulkier 1,4-benzoquinone derivatives, such as 2,6-dimethyl-1,4-BQ, 2,5-dimethyl-1,4-BQ or 2,3,5,6-tetramethyl-1,4-BQ (duroquinone), proved to be detrimental to both reactivity (15-29% conversion) and diastereoselectivity (*cis*/*trans* = 25:75-34:66, entries 3-5). These results suggest that the quinone acts as a ligand during the selectivity determining step as their increased steric hindrance

diminishes their coordinating ability to the palladium active species. In line with this hypothesis, the use of oxidants of profoundly different nature such as $Cu(OAc)_2$ or $K_2S_2O_8$ led to similar low conversion (below 30% in both cases) and poor diastereoselectivity (entries 6 and 7), whereas virtually no reaction was observed in the case of using $PhI(OAc)_2$ or TEMPO (< 5% conversion, entries 8 and 9).

Table 3.7: Evaluation of the role of 1,4-benzoquinone (BQ)



132 *cis*-**133** *trans*-**133**

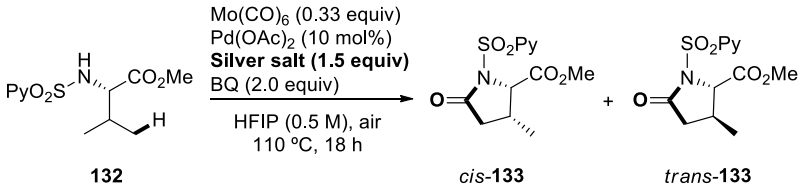
Entry	Oxidant	**133** Yield (%)[a]	*cis*/*trans* ratio[b]
1	-	15	30:70
2	BQ	86	16:84
3	2,6-di-Me-BQ	21	27:73
4	2,5-di-Me-BQ	29	34:66
5	Duroquinone[c]	15	25:75
6	$Cu(OAc)_2$	24	32:68
7	$K_2S_2O_8$	28	26:74
8	$PhI(OAc)_2$	< 5	-
9	TEMPO	< 5	-

[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *cis*/*trans* ratio determined by ^{1}H NMR spectroscopy from the crude mixture; [c] Duroquinone = 2,3,5,6-tetramethyl-1,4-benzoquinone.

- ***Evaluation of the role of the silver salt***

We next examined a set of silver salts as co-oxidants in order to gain insights about the effect of the nature of the counter anion on the reaction efficiency (Table 3.8). First, the control experiment in the absence of this co-oxidant, produced just a 9% conversion of the expected product **133**, which clearly illustrates the essential role that this species plays for the success of the reaction (entry 1). Among the wide number of silver salts tested, none of them improved our initial results obtained with AgOAc, thus evidencing the importance of the acetate ion, necessary for the reaction to proceed. For instance, the replacement of AgOAc with $Ag(O_2CCF_3)$ led to almost suppression of the catalytic activity (just 8% conversion) likely due to the lower basicity of trifluoroacetate compared to acetate (entry 3). Along with this line of argument, the catalytic activity was partially restored (42% conversion) when AgOBz was used as oxidant (entry 4). This silver salt bears a counter-anion (benzoate) significantly more basic than trifluoroacetate but still less basic than acetate, which could justify its intermediate reactivity. The use of AgOTf completely inhibited the reaction (entry 5) while silver salts with less coordinating counter-anions such as $AgSbF_6$ or Ag_2CO_3 led to the desired product in poor conversion (11 and 24%, respectively, entries 6 and 7). Finally, no reaction at all was observed when $Cu(OAc)_2$ was used instead of AgOAc (entry 8), suggesting that both the silver and the acetate ion are required as essential elements of the catalyst system.

Table 3.8: Evaluation of silver and copper salts as co-oxidants



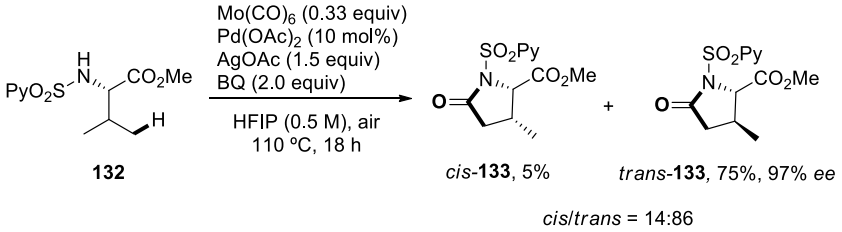
132 *cis*-**133** *trans*-**133**

Entry	Co-oxidant	**133** Yield (%)[a]	*cis*/*trans* ratio[b]
1	-	9	28:72
2	AgOAc	86	16:84
3	$Ag(O_2CCF_3)$	8	27:73
4	AgOBz	42	24:76
5	AgOTf	< 5	-
6	$AgSbF_6$	11	30:70
7	Ag_2CO_3	24	29:71
8	$Cu(OAc)_2$	< 5	-

[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *cis*/*trans* ratio determined by ^{1}H NMR spectroscopy from the crude mixture.

Unfortunately, this exhaustive evaluation of the different reaction parameters did not allow us to further improve our original conditions. However, these optimization experiments revealed important insights about the crucial role of each component of the catalyst system. Therefore, optimized conditions were established which entailed the treatment of the amino ester derivative **132** with 10% of $Pd(OAc)_2$, 0.33 equiv of $Mo(CO)_6$, 2.0 equiv of 1,4-benzoquinone, 1.5 equiv of AgOAc in HFIP as solvent (0.5 M) to provide a 86% conversion towards the γ-lactam **133** as a 16:84 separable mixture of *cis*- (5% isolated yield) and *trans*- (75% isolated yield) diastereoisomers after 18 h at 110 ºC (Scheme 3.47).

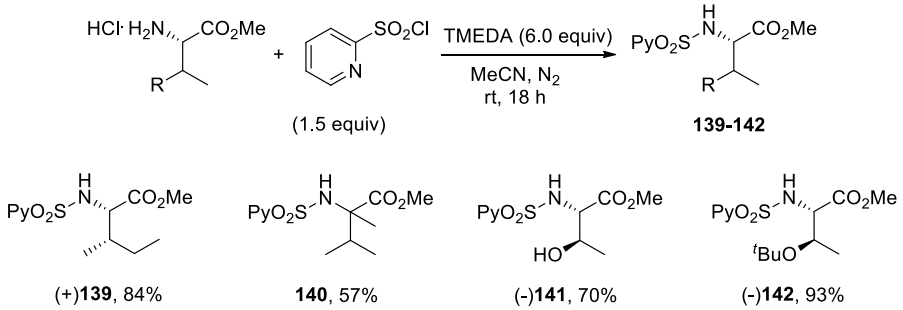
Final optimized conditions for the carbonylative cyclization reaction of 132



Scheme 3.47

3.7.3. Structural versatility of the γ-C(sp^3)–H carbonylation reaction

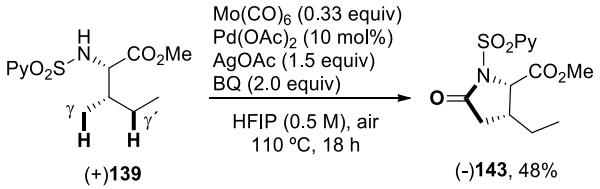
Having established an efficient catalytic system for the selective γ-C(sp^3)–H carbonylation/cyclization reaction, we set out to investigate the versatility of the reaction with regard to modifications in the amino acid moiety. For that purpose, differently substituted amino acid derivatives (**139-142**) were synthesized in moderate to excellent yields (57-93%) following the standard *N*-sulfonylation protocol from the corresponding commercially available amino acid methylester hydrochlorides (Scheme 3.48).



Scheme 3.48

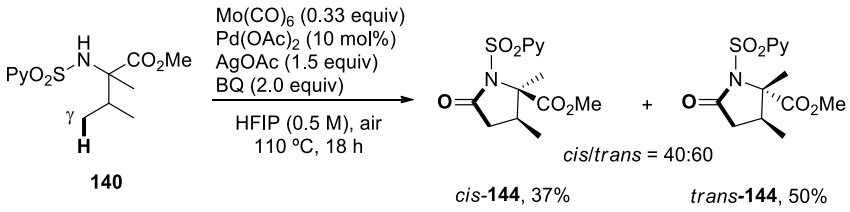
All these *N*-(2-pyridyl)sulfonyl amino acid derivatives (**139-142**) were thus subjected to our C–H carbonylation protocol under the optimized reaction conditions.

The reaction of derivative (+)**139**, having two sterically distinct primary and secondary γ-C(sp^3)–H bonds, selectively produced cyclized product (-)**143** (48%) indicating that primary (methyl) γ-C(sp^3)–H bonds are more reactive in comparison with secondary (methylene) ones under this catalyst system.



Scheme 3.49

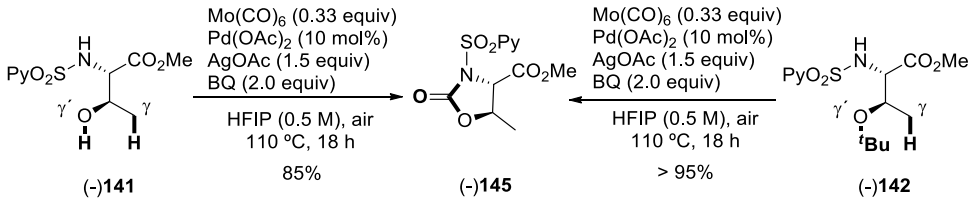
Derivative **140**, bearing a quaternary center at the α-position, did also participate in the reaction, yielding the expected cyclized compound **144** as a separable 40:60 mixture of *cis*/*trans* diastereoisomers in good yield [overall yield = 87%, (37% for *cis*-**144** and 50% for *trans*-**144**)]. Both diastereoisomers could be unambiguously assigned by NOE correlation experiments as depicted in Figure 3.5. When Me^4 was selectively irradiated, a strong NOE correlation was observed between Me^4-Me^5 in the case of *trans*-**144** (1.15%) indicating that both methyl groups are oriented in the same face of the molecule, while in the case of *cis*-**144** the NOE correlation presented a value of 0.56%, indicating a *trans*-arrangement of both methyl groups.



Scheme 3.50

Figure 3.5

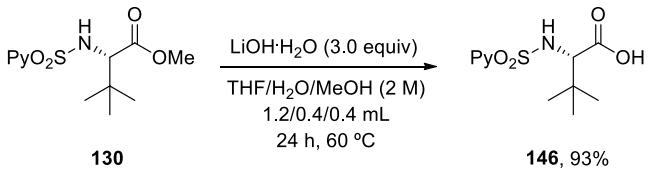
Not unexpectedly, carbonylation of the threonine derivative (-)**141**, having at the γ-position with regard to the sulfonamide group two types of reactive C–H and O–H bonds, led to the clean formation of the cyclic carbamate (-)**145**, as a result of a hydrocarboxylation rather than a C–H carbonylation. Product (-)**145** was obtained in good yield (85%) with no sign of the γ-lactam formation. In an attempt to avoid the O–H carbonylation and direct the reaction to the γ-C(sp^3)–H bond, we decided to use as starting material the threonine derivative (-)**142**, presenting the hydroxyl group protected as the corresponding *tert*-butyl ether.[214] However, when the *O-tert*-butyl derivative (-)**142** was submitted to the standard carbonylation conditions, the carbamate (-)**145** was quantitatively produced as the only reaction product (95% yield). This result evidences that the *tert*-butyl ether protecting group is not able to survive these reaction conditions and is in line with the previously observed lability of the *L*-valine *tert*-butyl ester derivative **138** (see Scheme 3.45).



Scheme 3.51

[214] Product **142** is readily prepared from the commercially availble *O-tert*-butyl-*L*-threonine methyl ester hydrochloride by simple *N*-sulfonylation.

Based on some precedents reported in the literature showing that free carboxylic acid moieties are amenable to C(sp^3)–H functionalization,[215] we envisioned that α-amino acid derivatives containing a free carboxylic acid entity could also be applicable to our optimized carbonylation protocol. To test this possibility, the *tert*-leucine derivative **146** was readily prepared from **130** by simple basic hydrolysis of the methyl ester group following a reported procedure (treatment with $LiOH{\cdot}H_2O$ in a 2 M THF/H_2O/MeOH mixture for 24 h at 60 ºC).[216] The expected carboxylic acid product **146** was thus obtained in 93% yield upon simple acid-base extraction without need for chromatographic purification (Scheme 3.52).



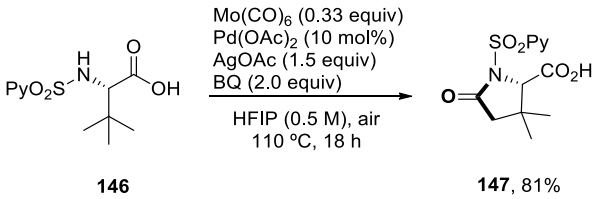
130 **146**, 93%

Scheme 3.52

Interestingly, compound **146** proved to be a suitable substrate for our carbonylation reaction, yielding the expected 5-oxopyrrolidinone-2-carboxylic acid derivative **147** in good yield (81%), thus expanding the functional group tolerance of this method to free carboxylic acid (Scheme 3.53).

[215] For a selected review on the carboxylate-directed C–H functionalization, see: G. Shi, Y. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 1419.

[216] For selected examples on the ester moiety hydrolysis using these reaction conditions, see: a) F. Kolundzic, M. N. Noshi, M. Tjandra, M. Movassaghi, S. J. Miller, *J. Am. Chem. Soc.* **2011**, *133*, 9104. b) D. Hernández, E. Riego, A. Francesch, C. Cuevas, F. Albericio and M. Álvarez, *Tetrahedron* **2007**, *63*, 9862.



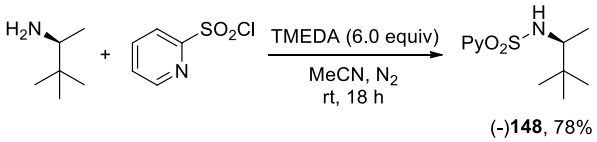
146 **147**, 81%

Scheme 3.53

3.7.4. Extension of the method to simple *N*-(2-pyridyl)sulfonyl-protected amines

The broad substrate scope displayed by this reaction with α-amino acid derivatives prompted us to explore the extension of this method to simple aliphatic amine derivatives. Additionally, this type of substrates, lacking a α-carboxylate ester/carboxylic acid group would allow us to evaluate whether the presence of such potentially coordination functionalities had an effect on this transformation.

As a starting point, compound (-)**148**, analogue to *tert*-leucine derivative **130** but lacking the methyl ester moiety, was considered as model substrate to test whether or not the C–H activation process is compatible with simple amine derivatives. Enantiomerically pure (-)**148** was efficiently prepared from the commercially available (*S*)-(+)-3,3-dimethyl-2-butylamine following the typical *N*-sulfonylation procedure and was isolated in good yield (78%) as a bench-stable white solid (Scheme 3.54).



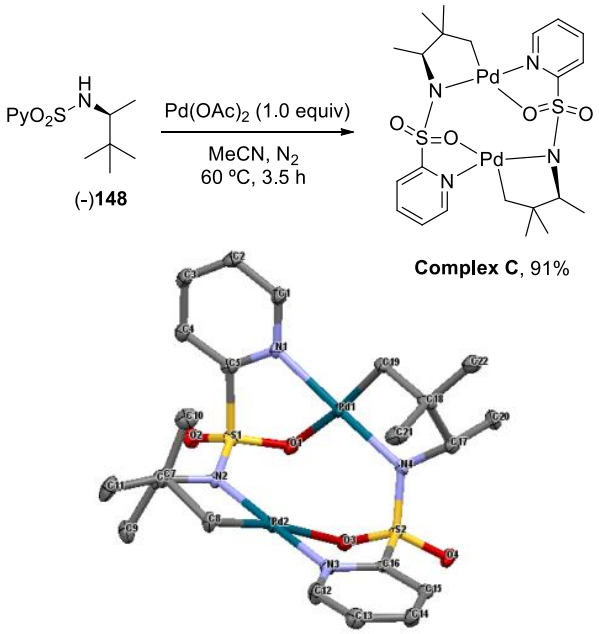
(-)**148**, 78%

Scheme 3.54

Next, we decided to see if this compound could undergo cyclometallation at the γ-C(sp^3)–H bond, leading to a palladium complex similar to the bimetallic **complex A**

previously obtained from the *tert*-leucine derivative **130**, and if such resulting complex display comparable stability to that of **complex A**.

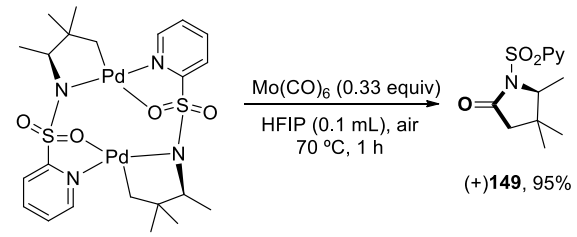
The stoichiometric reaction of (-)**148** with $Pd(OAc)_2$ (1.0 equiv) in acetonitrile at 60 ºC for 3.5 h, cleanly provided, after simple recrystallization (DCM/hexane), the expected bimetallic **complex C** in 91% yield, which presents an analogous structure to **complex A**. The structure of this new complex was unambiguously determined by single crystal X-Ray diffraction analysis after achieving suitable crystals by slowly evaporation of a MeCN/hexane solution of (-)**148** (Scheme 3.55).



Scheme 3.55

The synthesis of the bimetallic **complex C** demonstrated that the ester group at the α-position of the previously studied α-amino ester derivatives had no influence on the C–H activation step. Furthermore, the reaction of this complex with 0.33 equiv of $Mo(CO)_6$ at 70 ºC in 0.1 mL of HFIP for 1 h afforded the expected γ-lactam product (+)**149** in 95% yield, evidencing that simple *N*-(2-pyridyl)sulfonyl-protected aliphatic

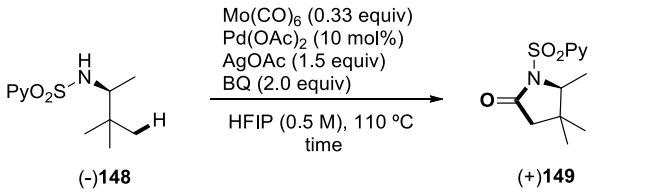
amines also serve as suitable substrates for the γ-C(sp^3)–H carbonylative cyclization protocol (Scheme 3.56).



Complex C (0.013 mmol)

Scheme 3.56

We next focused on developing a catalytic rather than stoichiometric version of this process. To our delight, when (-)**148** was subjected to the optimized reaction conditions, pyrrolidinone (+)**149** was cleanly obtained in 89% yield. In order to demonstrate the practicality of our method we performed the same experiment on a larger scale. As shown in Scheme 3.57, the expected product was achieved in a similarly high yield (85%) and only extending the reaction time from 18 h to 24 h was required.

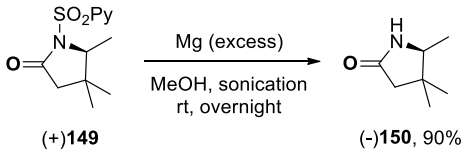


(-)**148** (+)**149**

mmol	time (h)	isolated yied
0.10	18	89
3.73 (***1.0 gram***)	24	85

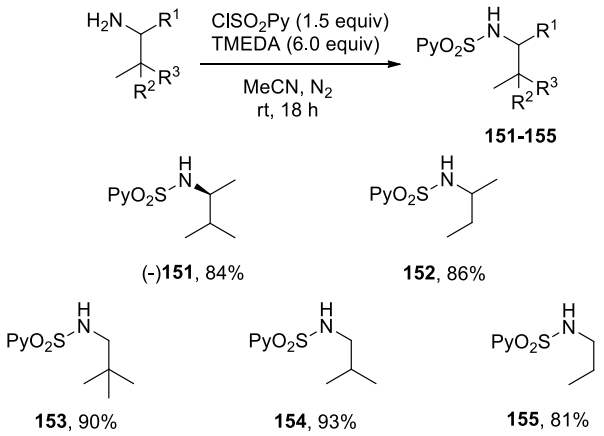
Scheme 3.57

At this point, we confirmed that the (2-pyridyl)sulfonyl directing group can be easily removed from the carbonylation γ-lactam products under mild conditions. For example, treatment of (+)**149** with magnesium turnings in MeOH at rt under sonication overnight, afforded the expected deprotected derivative (-)**150** in 90% yield.



Scheme 3.58

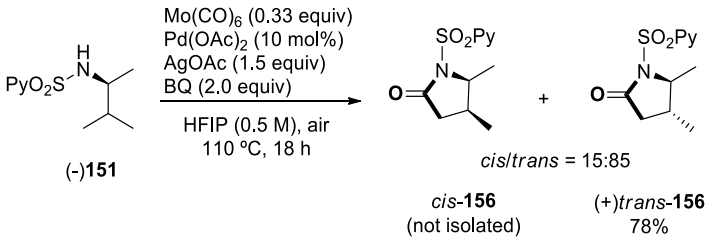
Encouraged by this result, showing good structural tolerance of our catalyst system, the scope of simple aliphatic amine derivatives was next evaluated. To study the versatility of the reaction with regard to steric modifications of the reactive γ-C(sp^3)–H bond, *N*-(2-pyridyl)sulfonyl-protected amines **151-155** were prepared in excellent yields (81-93%) by standard *N*-sulfonylation of the corresponding commercially available aliphatic amines (Scheme 3.59).



Scheme 3.59

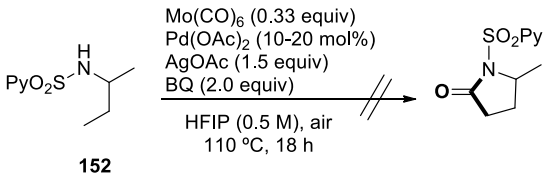
- ***Effect of branching at the β-position***

The reaction of (-)**151**, possessing two diastereotopic β-methyl groups led to the expected 2-pyrrolidinone **156** in 78% yield as mixture of diastereoisomers with moderate selectivity in favour of the *trans*-derivative (78% isolated yield of (+)*trans*-**156**, *cis*/*trans* = 15:85, Scheme 3.60).



Scheme 3.60

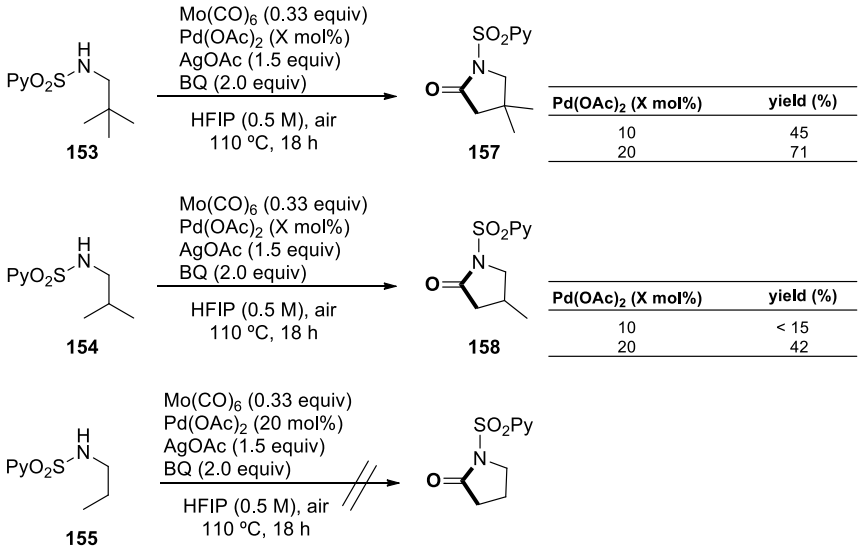
In sharp contrast, the 2-butanamide derivative **152,** without branching at the β-position resulted unproductive under the reaction conditions even when increasing the catalyst loading to a 20 mol% of $Pd(OAc)_2$ with most of the starting material recovered along with a tiny amount (< 10%) of an unidentified product (Scheme 3.61). These results suggest that branching at the β-position is an essential biasing structural element for the reaction to proceed.



Scheme 3.61

- ***Effect of branching at the α-position***

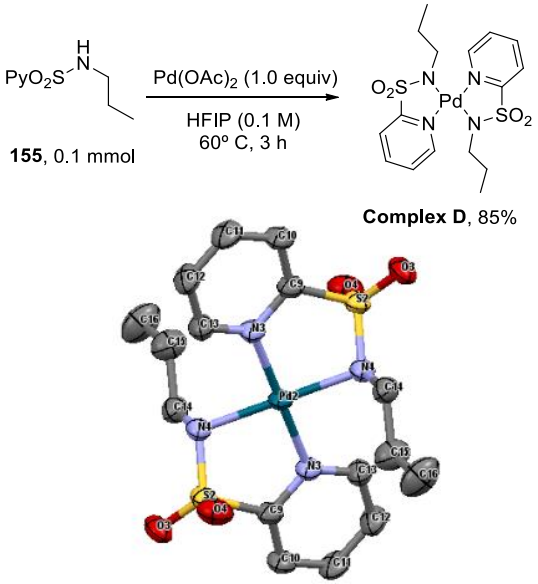
We were pleased to find that branching at the α-position was not a required structural feature for this transformation, even though this type of substitution is often necessary as turning elements maximizing the conformation that leads to C–H activation. Nevertheless, the reaction proved to be more difficult, requiring an increased catalyst loading of 20 mol% to achieve synthetically useful yields. For instance, the carbonylative cyclization of the 2,2-dimethylpropanamine derivative **153** afforded the 4,4-dimethyl-2-pyrrolidinone derivative **157** in good yield (71%). On the other hand, the less conformationally restrained derivative **154** was found to be significantly less reactive, providing the corresponding 4-methyl-2-pyrrolidinone **158** in an acceptable 42% yield under identical reaction conditions. In accordance with these observations, the linear propanamine derivative **155** , having unbranched both α- and β-positions was unreactive towards the C–H carbonylation and only trace amounts (roughly 10%) of an identified product was observed in the reaction mixture along with the recovered starting material, as encountered earlier in the case of **152**.



Scheme 3.62

Intrigued by the strong dependence of the reactivity on the steric properties disposed by the substitution pattern of the substrates and the appearance of an unknown product in the reaction of amine derivatives lacking any substituent at the β-position (starting compounds **152** and **155**), we decided to study in more detail the cause behind this effect. A scan of the literature revealed that most secondary amines rapidly form square-planar, coordinately saturated bis-amine palladium(II) complexes when treated with palladium(II) salts.[217] Thus, it is reasonable to assume the formation of this type of bis-amine complexes in the reaction of the secondary sulfonamides used in this study with $Pd(OAc)_2$. Moreover, the *N*,*N*-bidentate nature of these substrates imported by the 2-(pyridyl)sulfonyl protecting/directing group should strengthen the interaction of the substrate to the metal, thereby compensating the weaker donor ability of sulfonamide compared to amine ligands, leading to more stable complexes. To test this hypothesis, the linear propanamide derivative **155** was treated with a stoichiometric amount of palladium(II) acetate (Scheme 3.63). After 3 h of reaction in HFIP at 60 ºC, we observed by ^{1}H NMR the clean formation of the mononuclear palladium **complex D**, which was isolated in 85% yield as an air-stable orange solid upon simple crystallization in CH_3CN/hexanes. X-ray diffraction analysis of suitable crystals revealed a slightly distorted square-planar *N*,*N*,*N*,*N*-tetracoordinated palladium complex in which the Pd^{II} atom coordinates two molecules of **155** through the deprotonated amide and the pyridyl nitrogen atoms, with slightly longer bonds between the Pd^{II} and the amide nitrogen (2.056 Å) than those between Pd^{II} and the pyridine nitrogen atoms (2.038 Å).

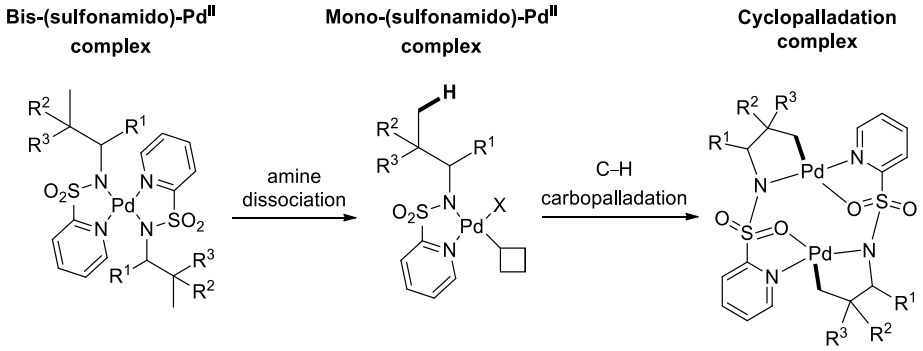
[217] A. D. Ryabov, *Chem. Rev.* **1990**, *90*, 403.



Scheme 3.63

The formation of this type of stable square-planar, coordinately saturated Pd-complex provides a reasonable explanation for the strong dependence of reactivity on the degree of substitution (branching) of the substrate. In fact, **complex D** was determined to be the by-product observed accompanying the starting material in the failed Pd-catalyzed carbonylation reaction of amine derivative **155** described previously in Scheme 3.62. Once this bis-sulfonamido Pd^{II}-complex is formed, the pathway for subsequent C–H bond functionalization requires liberation of a coordination site occupied by one of these sulfonamides. If the palladium(II) complex formed is very stable, there is little driving force for the release of an amide ligand thus rendering the bis-amido palladium species catalytically inactive. The lack of reactivity observed for β-unbranched substrates **152** and **155** can be plausibly explained by the increased stability of the formed Pd^{II} intermediate complexes. The more hindered secondary sulfonamides explored, which contain substitution at the β- (and α-) positions also form the corresponding bis-amido complexes with Pd(OAc)$_2$; however, we propose that in these cases the increased steric hindrance

around the Pd^{II} center results in more facile ligand dissociation. This weaker binding would therefore facilitate the release of one of the sulfonamides to create the essential vacant coordination site [mono(sulfonamido)-Pd^{II} complex] and enable the C–H activation to take place (Scheme 3.64).[218] The fact that amine derivatives branched at both the α- and β-positions displayed the best results and the higher reactivity of substrate **153**, with a fully substituted β-carbon, over amine derivative **154**, with a tertiary β-carbon, provides further support to our proposal.



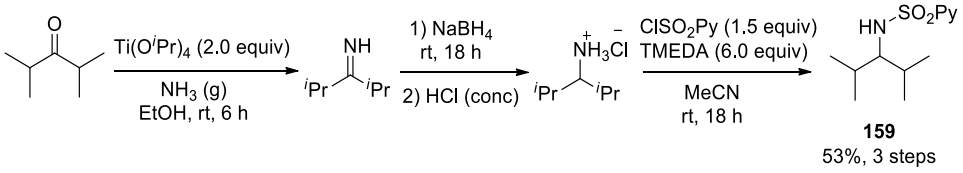
Scheme 3.64

- ***Desymmetrization of an achiral acyclic amine derivative***

Additionally, we found interesting to test the achiral symmetric amine derivative **159**, whose carbonylative cyclization would lead to a chiral γ-lactam bearing two contiguous stereogenic centers. However, unfortunately, the corresponding 2,4-dimethyl-3-pentanamine was not commercially available and had to be prepared in a three-step procedure from 2,4-dimethyl-3-pentanone (Scheme 3.65). In a first reaction step, this ketone was transformed into its NH-imine derivative by a $Ti(OiPr)_4$-promoted imination using gaseous ammonia. Subsequent reduction of the imine with $NaBH_4$ and treatment of the resulting amine with concentrated HCl yielded

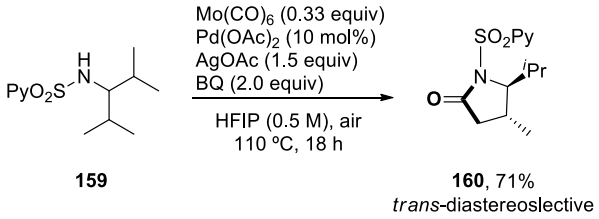
[218] For a review on the importance of week coordination in C–H functionalization reactions, see: K. M. Engle, T. –S. Mei, M. Wasa, J. –Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788.

the corresponding amine hydrochloride salt, which was subsequently submitted to the standard *N*-sulfonylation with 2-PySO$_2$Cl, to afford the expected *N*-(2-pyridyl)sulfonyl-protected amine derivative **159** in a 53% overall yield (for three steps).



Scheme 3.65

When substrate **159** was tested in the γ-C(sp^3)–H carbonylation reaction, the 5-isopropyl-4-methyl-2-pyrrolidinone derivative **160** was obtained in good yield (71%) as a single diastereoisomer with *trans*-relative configuration (Scheme 3.66). The complete *trans*-diastereoselectivity achieved in this case is likely due to the disparate steric properties of the methyl and the isopropyl groups.



Scheme 3.66

The *trans*-relative configuration of pyrrolidinone **160** was unambiguously established from the NOE NMR correlation experiments. Thus, the stronger NOE correlation between H^5 and Me^4 (1.98%) than that between H^4 and H^5 (0.74%) suggests that H^5 and Me^4 are oriented to the same side of the molecule. Additionally, the *iso*-propyl group did not present any correlation with Me^4, which indicates that these functional groups present a *trans*-relative configuration (Figure 3.6).

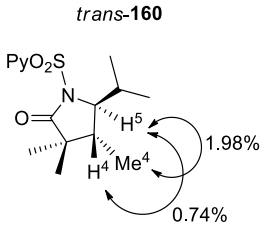


Figure 3.6

3.7.5. Extension to carbonylation at γ-methylene groups of aliphatic amine derivatives

- ***C–H carbonylation of cyclopropylmethylamine derivatives***[219]

These encouraging results demonstrating that simple aliphatic amines can efficiently be carbonylated at the γ-CH_3 group, drew our attention to examine the feasibility of extending the reaction to the more challenging (less reactive) γ-methylene C–H bonds.

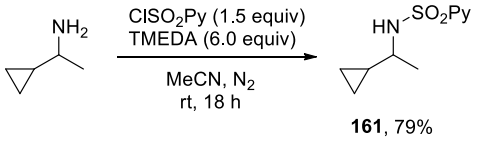
In particular, given the prominence of cyclopropanes in natural products and pharmaceuticals[220] along with the scarcity of methods enabling C–H activation of cyclopropanes,[221] we sought to develop a procedure for the C–H carbonylation of

[219] Part of the carbonylation studies of cyclopropane derivatives have been performed in collaboration with the undergraduate student Julia Villalva.

[220] For the medicinal chemistry of biologically active cyclopropane derivatives, see: a) K. A. Kumar, *Int. J. Pharm. Pharm. Sci.* **2013**, *5*, 467. b) J. Salaün, M. S. Baird, *Curr. Med. Chem.* **1995**, *2*, 511. For a review on the use of cyclopropanes and their derivatives in organic synthesis, see: c) H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **1989**, *89*, 165.

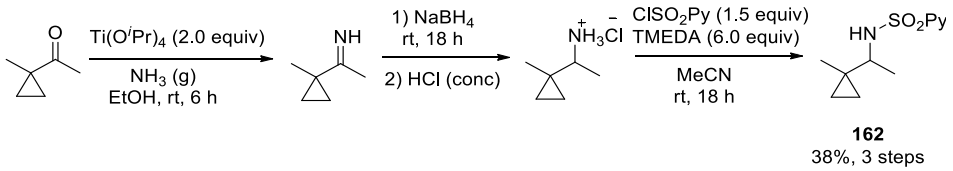
[221] For examples on the C(sp^3)–H functionalization of cyclopropane derivatives, see: a) D. S. Roman, A. B. Charette, *Org. Lett.* **2013**, *15*, 4394. b) R. Parella, B. Gopalakrishnan, S. A. Babu, *Org. Lett.* **2013**, *15*, 3238. c) M. Wasa, K. M. Engle, D. W. Lin, E. J. Yoo, J. –Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19598. Very recently, during the process of writing this Ph.D. Thesis manuscript, a Pd-catalyzed enantioselective C–H arylation of cyclopropylmethylamine derivates has appeared in the literature, see: d) K. S. L. Chan, H. –Y. Fu, J. –Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 2042.

cyclopropane derivatives which, to the best of our knowledge, remained undocumented to the date. Additionally, a unique structural feature of cyclopropanes provided further motivation for us to use cyclopropylmethylamine derivatives as substrates: the rigidity of the cyclopropyl ring and orbital hybridization leads to a more sp^2-like character for its carbon atom, which should facilitate C–H functionalization processes. To this end, the cyclopropylmethylamine derivatives **161** and **162**, the latter containing both a γ-CH_3 and a γ-methylene cyclopropyl moiety, were envisaged as representative substrates. Product **161** was readily prepared by simple *N*-protection of the commercially available 1-cyclopropylethylamine in 79% isolated yield (Scheme 3.67).



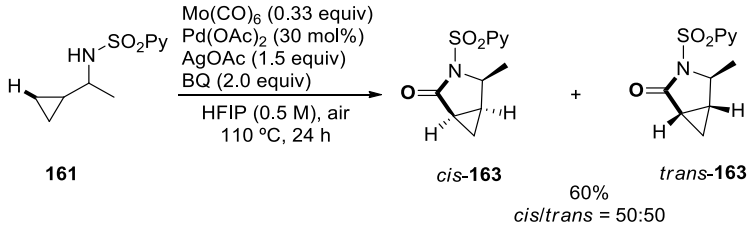
Scheme 3.67

Its analogue **162**, whose amine was not available from commercial sources, was prepared from the commercially available ketone as previously described (Scheme 3.68). The titanium tetraisopropoxide-mediated imine formation between the ketone and ammonia in ethanol, followed by *in situ* reduction with sodium borohydride led to the formation of the corresponding amine, which was isolated as its chlorhydrate upon treatment with concentrated hydrochloric acid. Subsequent *N*-sulfonylation with (2-pyridyl)sulfonyl chloride under standard conditions led to the expected cyclopropyl-containing sulfonamide **162** in an overall 38% yield (unoptimized).



Scheme 3.68

When derivative **161** was submitted to the optimized carbonylation reaction conditions, less than a 10% of conversion to the expected cyclopropane-fused pyrrolidinone derivative **163** was detected by ^{1}H NMR in the crude mixture. However, to our satisfaction, increasing the Pd-catalyst loading from 10 mol% to 30 mol% dramatically improved the conversion to 69%, allowing the product **163** to be isolated in 60% yield as a 50:50 mixture of *cis*/*trans* diastereoisomers that could not be separated by conventional column chromatography (Scheme 3.69).[222]

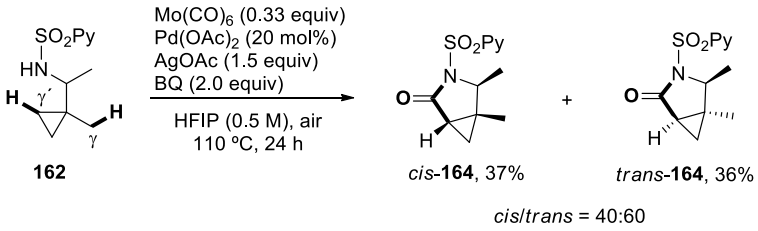


Scheme 3.69

Interestingly, under similar reaction conditions [in this case the Pd(OAc)$_2$ catalyst loading could be reduced to 20 mol%], the β-methyl-substituted analogue **162** was selectively functionalized at the methylene γ-C(sp^3)–H bond of the cyclopropyl substituent, yielding the cyclopropane-fused-pyrrolidinone derivative **164** in 73% yield

[222] The *cis*/*trans* notation refers to the relative orientation of the methyl group at C(5) of the 2-pyrrolidinone ring and the cyclopropane ring.

as a mixture of the two possible diastereoisomers in favour of the presumably thermodynamically *trans*-configured derivative (cis/trans = 40:60, Scheme 3.70).[223]



Scheme 3.70

Interestingly, this result shows that not only this method is effective for the carbonylation of methylene C–H bonds in cyclopropylmethylamine derivatives, but it also reveals that cyclopropyl C(sp^3)–H bonds can be selectively carbonylated over a methyl C(sp^3)–H bond.

The difficulty in the chromatographic separation of the two fused diastereoisomers *cis*-**164** and *trans*-**164** prevented the isolation of each isomer in reasonable yield. However, partial separation provided sufficient amount of pure compounds to allow for characterization of each one by NMR methods. In particular, their *cis*/*trans* relative configuration was unambiguously established from ^{1}H-^{1}H NOE NMR experiments, being diagnostic the much stronger NOE correlation between Me^4 and H^5 found in *trans*-**164** (1.27 %) than that observed between Me^4 and H^5 in *cis*-**164** (0.17 %), clearly indicating that in the former case Me^4 and Me^5 are in relative *trans*-arrangement, whereas in the latter case both groups are in relative *cis*-orientation (Figure 3.7).

[223] The *cis*/*trans* notation refers to the relative orientation of the methyl groups at C(4) and C(5) of the 2-pyrrolidinone ring.

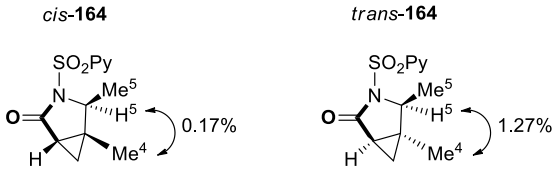
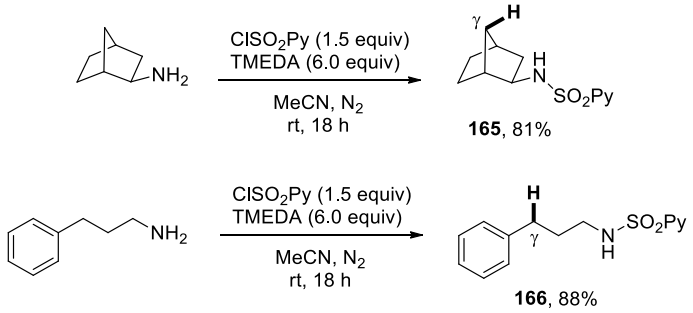


Figure 3.7

- ***C–H carbonylation of "normal" methylene C(sp^3)–H bonds***

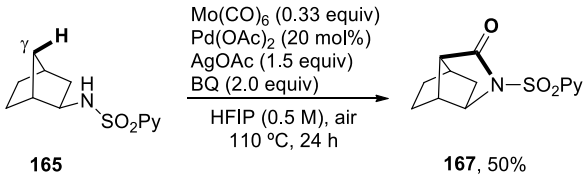
These results prompted us to explore the functionalization of "normal" methylene C(sp^3)–H bonds, without a marked sp^2 character as in cyclopropanes, such as those γ-C(sp^3)–H bonds found in the much sterically strained (±)-exo-norbornylamine derivative **165** and the acyclic chain of phenylpropylamine derivative **166**. Both substrates were prepared in good yields (81% and 88%, respectively), by simple *N*-sulfonylation of the corresponding commercially available amines as shown in Scheme 3.71.



Scheme 3.71

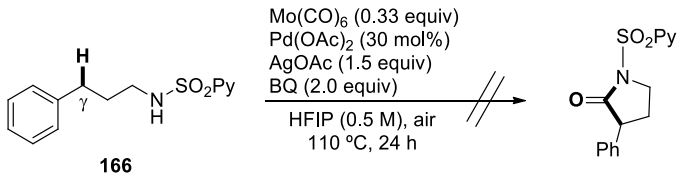
The carbonylation reaction of (±)-exo-norbornylamine derivative **165** afforded the expected C–H γ-carbonylated product **167** with incomplete conversion (75%) but allowed this product to be isolated in a synthetically useful 50% yield (Scheme 3.72). In contrast, the phenylpropylamine derivative **166** resulted totally unreactive (the starting material was fully recovered) when subjected to the carbonylation reaction

conditions, even when the $Pd(OAc)_2$-catalyst loading was further increased to 30 mol% (Scheme 3.73). The lack of reactivity of substrate **166** may arise from the absence of any substitution (branching) at either the α- or β-positions, which was found to be essential (especially branching at the β-position) for the reaction to proceed as demonstrated in our previous structural studies with simple aliphatic amines to prevent the formation of stable, catalytically inactive, coordinately-saturated bis-amido Pd^{II}-complexes (see Scheme 3.63). Therefore, further work testing analogue substrates with at least β-substitution is needed to get a more conclusive result on whether or not methylene γ-C–H bonds at acyclic chains do participate in this carbonylation reaction.



165 **167**, 50%

Scheme 3.72



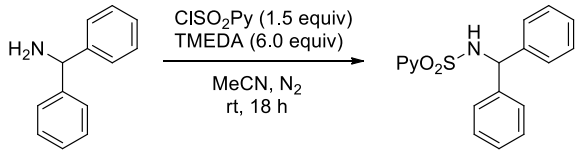
166

Scheme 3.73

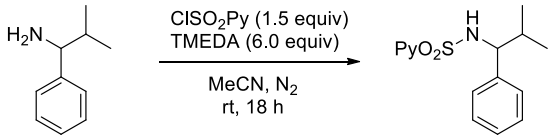
3.7.6. C(sp^2)–H *versus* C(sp^3)–H carbonylation

At this point, we wondered whether this method would be also effective for the C(sp^2)–H carbonylation of amine derivatives having an aromatic C–H bond at the γ-position. To test this possibility, the diphenylmethanamine derivative **168** bearing two aryl γ-C–H bonds and the 2-methyl-1-phenyl-1-propanamine derivative **169**,

containing both γ-C(sp^2)–H bond and γ-C(sp^3)–H bonds in its structure, were efficiently prepared from the corresponding amines (commercially available) by standard *N*-sulfonylation with (2-pyridyl)sulfonyl chloride under basic conditions (Scheme 3.74).



168, 89%



169, 79%

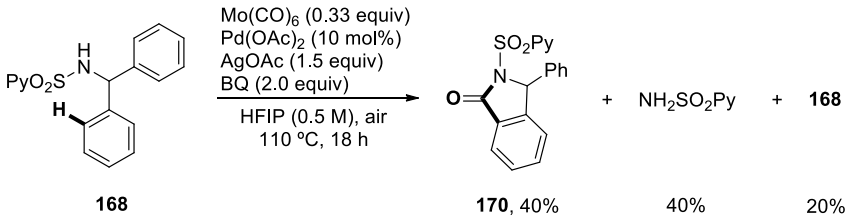
Scheme 3.74

The carbonylation reaction of diphenylmethanamine **168** under the optimized reaction conditions [$Pd(OAc)_2$ (10 mol%)] afforded the expected 3-phenylisoindolinone **170** in only 38% yield (40% ^{1}H NMR conversion), accompanied by a 20% of the starting material **168** and a 40% of (2-pyridyl)sulfonamide (Scheme 3.75). We attribute the partial failure of this transformation to the propensity of the diphenylmethanamine to undergo competitively dehydrogenation at the benzylic position under the oxidative reaction conditions, potentially leading to imine-type intermediates,[224] whose hydrolysis would lead to the (2-pyridyl)sulfonamide (along with benzophenone).[225] On the other hand, in previous C–H activation studies

[224] a) D. –S. Kim, J. –W. Park, C. –H. Jun, *Adv. Synth. Catal.* **2013**, *355*, 2667. b) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2013**, *40,* 600.

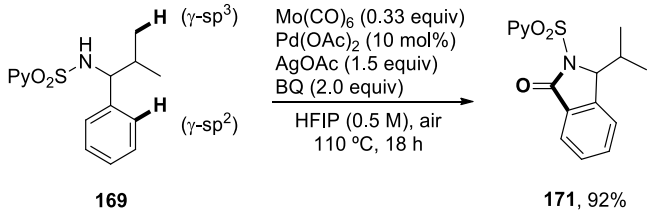
[225] No signals clearly attributed to benzophenone were identified in the ^{1}H NMR spectra due to the complexity of the aromatic region of the crude reaction mixture.

developed in our research group, it had been observed that the free (2-pyridyl)sulfonamide forms a strong complex with $Pd(OAc)_2$ that causes inhibition of its catalytic activity, which might also account for the low yield of product **170** and the significant amount of starting material recovered.



Scheme 3.75

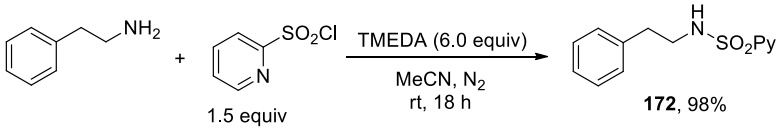
In contrast, the 2-methyl-1-phenylpropylamine derivative **169**, less prone to benzylic dehydrogenation, produced the corresponding 3-isopropylisoindolinone derivative **171** in an excellent 92% isolated yield when subjected to the standard optimized carbonylation conditions (Scheme 3.76). Interestingly, although this substrate has available an *ortho*-aryl C(sp^2)–H bond and six methyl C(sp^3)–H, all of them at the same relative γ-position, this substrate was site-selectively carbonylated at the more reactive C(sp^2)–H.



Scheme 3.76

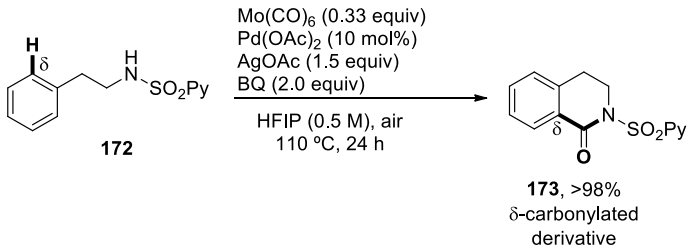
The high reactivity observed in the C(sp^2)–H carbonylation of the benzylamine substrate **169** prompted us to test the applicability of this methodology to

phenethylamine derivatives, having increased in one-atom the tether length of the directing group and, as a consequence, meaning that the activation must occur through higher palladacycle intermediates.[226] Phenethylamine was thus conveniently protected as *N*-SO_2Py sulfonamide (**172**) in high yield (98%).



Scheme 3.77

Delightfully, when derivative **172** was subjected the optimized reaction conditions, the δ-carbonylation product **173** was quantitatively achieved. This result evidences the formation of a six-membered palladacycle intermediate prior to CO insertion. This type of remote δ-functionalization is being studied in detail in our research group.



Scheme 3.78

[226] Inspired by the work of our research group, Yu and co-workers have reported the intramolecular C–H amidation of *N*-(2-pyridyl)sulfonyl phenethylamines leading to indoline derivatives, see: T. –S. Mei, D. Leow, H. Xiao, B. N. Laforteza, J. –Q. Yu, *Org. Lett.* **2013**, *15*, 3058.

3.7.7. Carbonylation/cyclization of di- and tri-peptides

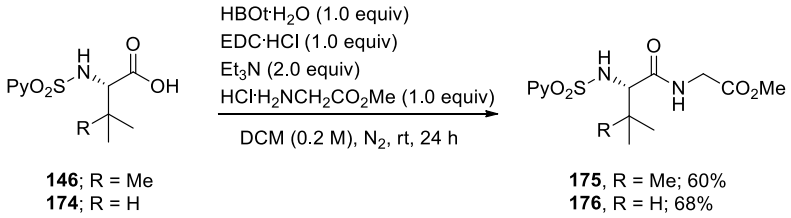
As mentioned earlier at the beginning of this chapter, because of the increasing interest in peptide therapeutics from the pharmaceutical industry, post-synthetic modification of peptides has emerged as a significant task.[131,132,150,168] This significance prompted us to investigate the direct carbonylation of di- and tri-peptides. The key question is whether those substrates will still be reactive toward C(sp^3)–H activation at the desired site even though the amino moiety embedded in these small peptides could form competing *N*,*N*- or *N*,*O*-bis-coordinated complexes with Pd^{II} that could compromise the desired reaction pathway. In other words, we were concerned that the additional coordinating amide bonds could inhibit the reaction. Indeed, Yu and co-workers have reported a number of Pd-catalyzed C–H activation procedures that rely on the use of mono-protected amino acids as ligands, thereby demonstrating their coordination ability to a Pd^{II} center.[227]

- ***C–H carbonylation of dipeptides***

Dipeptides **175** and **176** were synthesized by condensation of derivatives **146** and **174** with glycine methyl ester hydrochloride, following the well-established coupling protocol based on the use of HBOt·H_2O and EDC·HCl for activating the carboxylic groups and Et_3N as base.[228] The results are shown in Scheme 3.79.

[227] For selected recent examples on the use of amino acid derivatives as ligands (MPAA ligands), see: a) K. –J. Xiao, D. W. Lin, M. Miura, R. –Y. Zhu, W. Gong, M. Wasa, J. –Q. Yu, *J. Am. Chem. Soc.* **2014**, *136*, 8138. For mechanistic studies based on MPAA ligands, see: b) G. –J. Chen, Y. –F. Yang, P. Liu, P. Chen, T. -Y. Sun, G. Li, X. Zhang, K. N. Houk, J. –Q. Yu, Y. –D, Wu, *J. Am. Chem. Soc.* **2014**, *136*, 894. c) D. G. Musaev, A. Kaledin, B. –F. Shi, J. –Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 1690.

[228] For a mechanistic study on the coupling of carboxylic acids with amines using HBOt·H_2O and EDC·HCl, see: a) L. C. Chan, B. G. Cox, *J. Org. Chem.* **2007**, *72*, 8863. For a recent review on the development in peptide coupling reagents, see: b) T. I. Al-Warhi, H. M. A. Al-Hazimi, A. El-Faham, *J. Saudi Chem. Soc.* **2012**, *16*, 97.

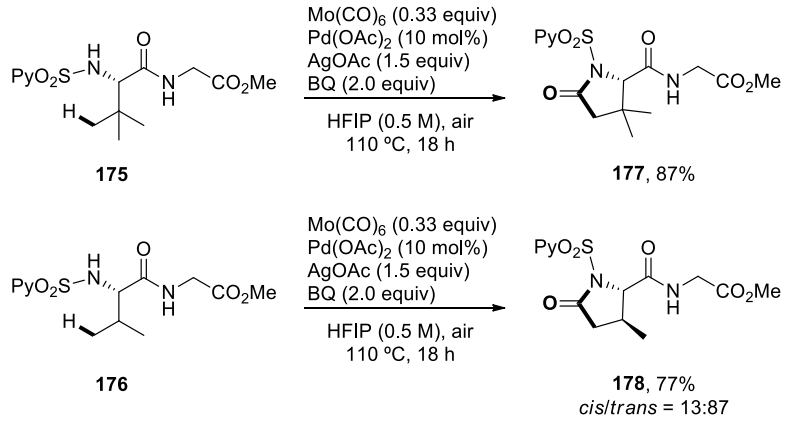


146; R = Me
174; R = H

175, R = Me; 60%
176, R = H; 68%

Scheme 3.79

These dipeptides were then subjected to our optimized reaction conditions for C–H carbonylation. We were glad to see that carbonylative cyclization of both *tert*-leucine-glycine (**175**) and valine-glycine (**176**) dipeptides took place efficiently providing the corresponding modified dipeptides **177** and **178** in very good yields (87% and 77%, respectively) and complete site-selectivity control after 18 h (Scheme 3.80). In both cases, virtually complete conversion was observed (95%); however, the difficulty in the chromatographic separation of the products from traces of starting material resulted in slightly reduced yields upon isolation. In the case of valine-containing dipeptide, the product **178** was obtained as a mixture of diastereoisomers with good *trans*-stereoselectivity (*cis*/*trans* = 13:87).



175

177, 87%

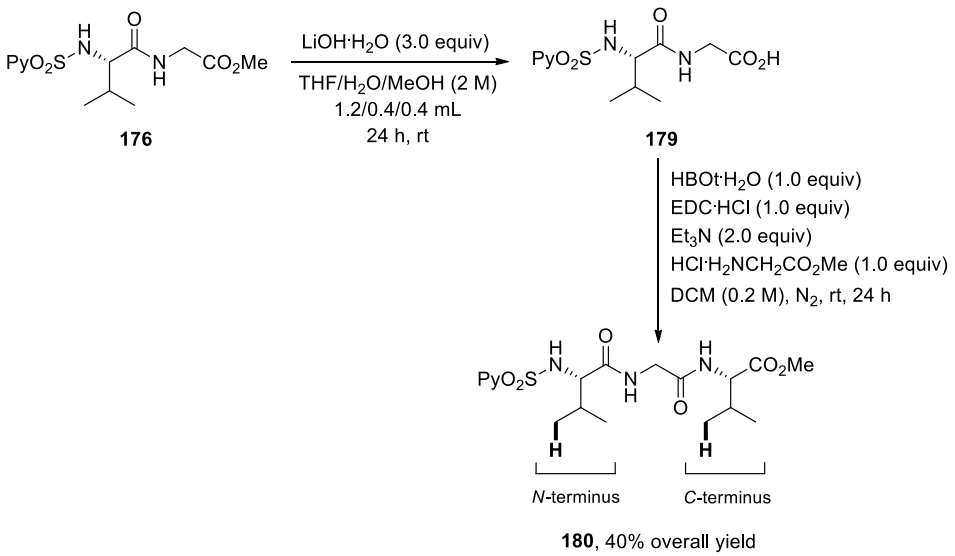
176

178, 77%
cis/*trans* = 13:87

Scheme 3.80

- ***C–H carbonylation of tripeptides***

Encouraged by the outstanding reactivity exhibited by our catalyst system in the direct carbonylation of dipeptide derivatives, we speculated about the possibility of broadening the applicability of this C–H bond carbonylation reaction to the more challenging tripeptide substrates. Following this idea, the tripeptide valine-glycine-valine **180** was synthesized in 40% overall yield (unoptimized) from the previously prepared valine-glycine dipeptide **176** (Scheme 3.81). The sequence started by saponification of the methyl ester moiety of **176** under basic conditions following the reported procedure.[216] The resulting carboxylic acid derivative **179** was readily isolated by acid/base extraction and directly subjected to the coupling reaction with *L*-valine methyl ester hydrochloride under the same reaction conditions used before for the dipeptide synthesis, affording the expected tripeptide derivative **180**.

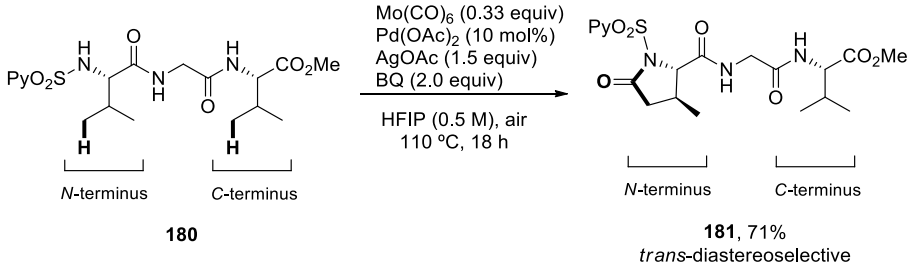


Scheme 3.81

A primary reason behind the selection of this particular tripeptide is that it contains two valine moieties, one at the *N*-terminus and another one at the

C-terminus. Considering that the *C*-terminus of the tripeptide is a native monoprotected amino acid that can also coordinate to the Pd^{II} species,[227] thus forming a reactive complex that could potentially activate the γ-C(sp^3)–H bond of the proximal valine unit, this substrate **180** is well suited to test the capability of the *N*-(2-pyridyl)sulfonyl directing group in controlling site-selectivity.

To our delight, the carbonylation of tripeptide **180** under the optimized reaction conditions proceeded smoothly to afford the expected modified tripeptide **181** as the only product in 71% yield after chromatographic purification. Importantly, the C–H activation occurred with complete site-selectivity control at the *N*-terminus, thus highlighting the key directing role of the *N*-(2-pyridyl)sulfonyl group. Also remarkable is that the tripeptide **181** was produced as a single stereoisomer with complete *trans*-diastereoselectivity, presumably due to the much bulkier peptide chain attached to C(5) of the 2-pyrrolidinone cyclic system, thus making more thermodynamically unstable the *cis*-stereoisomer (Scheme 3.82). Importantly, this study illustrates not only the functional group tolerance of our method, but also the capacity of the bidentate *N*-(2-pyridyl)sulfonyl directing group to override other inherent substrate coordinating elements such as peptide bonds (*via* *N*,*N*- or *N*,*O*-bis-dentate coordination). We anticipate that these findings could pave the way for further development of C–H bond functionalization of peptide aliphatic side chain in the context of post-synthetic modification of peptides.

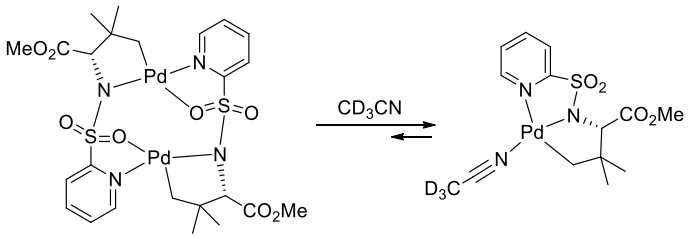


Scheme 3.82

3.7.8. Mechanistic insights

- **Behaviour of complex A in solution**

In order to gain insights into the reaction mechanism, we first sought to identify the catalytically active species. Thus, the nuclearity of the bimetallic **complex A** in solution was first investigated. Previous 1D-selective NOE experiments performed in our group on a CD_3CN solution of this complex[32b] strongly suggested that the dimer is not the predominant species in solution of CD_3CN, but rather this complex is mainly present as a monomer (most likely **A´**), in which the weakly coordinating CD_3CN reversibly coordinates the active catalyst (**A´**), effectively occupying the free coordination site necessary for the C–H bond cleavage (Scheme 3.83).



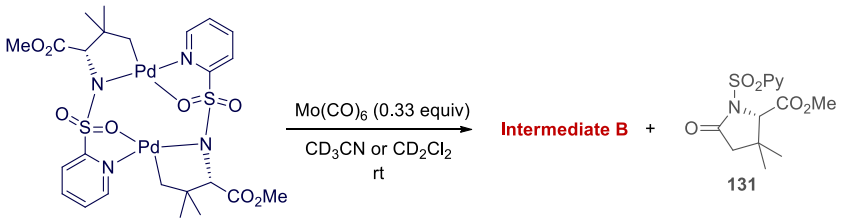
Complex A (dimeric) **Complex A´** (monomeric)

Scheme 3.83

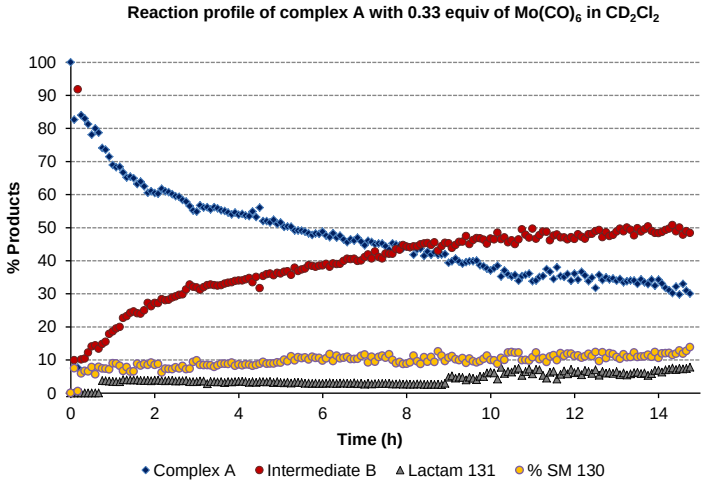
In accordance with these observations, a marked difference in the reactivity profile should be noticed when monitoring by ^{1}H NMR the direct, stoichiometric carbonylation of **complex A** with $Mo(CO)_6$ (0.33 equiv) using CD_2Cl_2 as solvent, compared to the results described earlier in CD_3CN (for the latter, see section 3.7.1; those data are also given here alongside for comparison purposes). As shown in Figure 3.8, which compares the reaction kinetic profiles from a measure of conversion (%) *versus* time (hours) in both CD_2Cl_2 and CD_3CN, the reaction in CD_2Cl_2 presented a much lower transformation of **complex A** into **intermediate B**, reaching a 50% conversion after 10-13 h, which stands in sharp contrast with the rapid

formation of **intermediate B** from **complex A** in CD_3CN (50% conversion upon 2.5 h). Additionally, in CD_2Cl_2 **intermediate B** showed increased stability, resisting decomposition towards the expected lactam γ-**131** along time (<10% conversion after 15 h),[229] whereas a relatively fast conversion of **intermediate B** into the final γ-**131** was observed in CD_3CN after an induction period of 2.5 h, with complete consumption of **intermediate B** upon 6.5 h of reaction.

[229] Under these conditions, a small amount of the decomplexated *L-tert*-leucine derivative **130** resulting from proto-demetallation was consistently observed in the reaction mixture (<15% upon 15 h).



Complex A



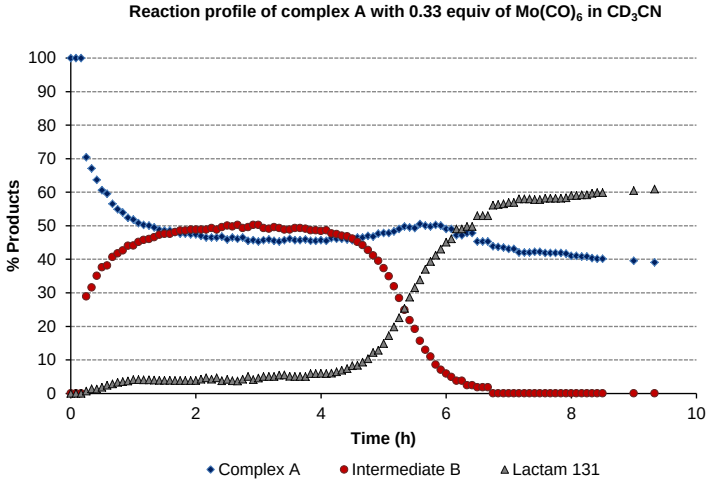


Figure 3.8

To further corroborate this hypothesis, we decided to perform an analysis by positive electrospray high resolution mass spectroscopy (ESI-HRMS) of two separate solutions of **complex A**, one in the weakly coordinating MeCN as solvent and another one in an apolar non-coordinating solvent such as DCM. The ESI-HRSM spectrum of **complex A** in MeCN is shown in Figure 3.9. The main feature of this spectrum is that it shows intense peaks corresponding to monomeric Pd^{II} complexes. In fact, the monomeric **complex A´** was detected as the most intense peak [m/z $(M+H)^+$: 432.0198], while the corresponding monomeric **complex A´´**, resulting from **A´** by loss of CH_3CN ligand, was also detected in lower abundance but with appreciable intensity [m/z $(M+H)^+$: 390.9872]. Instead, the dimeric form of this complex (**complex A**), easily attributable to the peak at m/z $(M+H)^+$: 780.9782, was detected with a very low intensity.

In comparison with the previous results, the ESI-HRMS analysis of a solution of **complex A** in DCM showed the dinuclear species (**A**) with the highest intensity, clearly indicating that this complex becomes predominant in non-coordinating solvents (Figure 3.10). No mononuclear species associated with this complex were detected in this case.

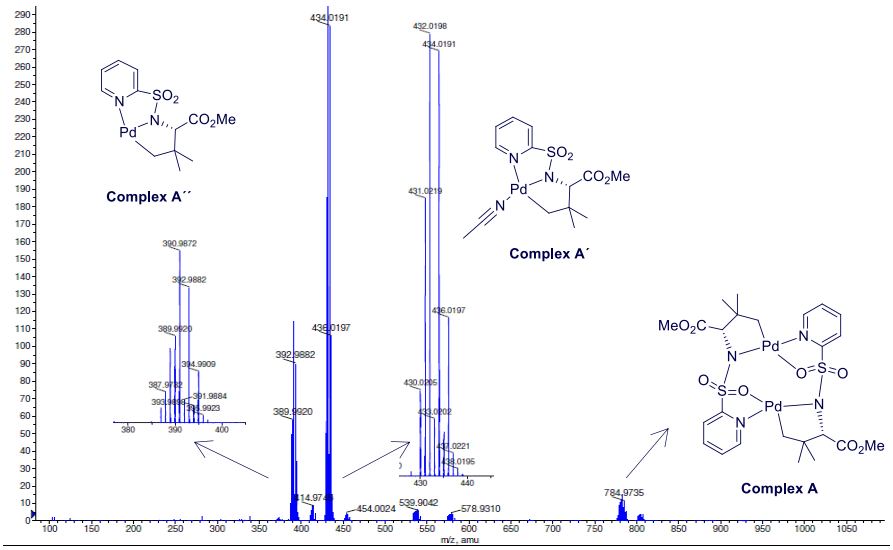


Figure 3.9: HRSM spectrum of complex A in MeCN

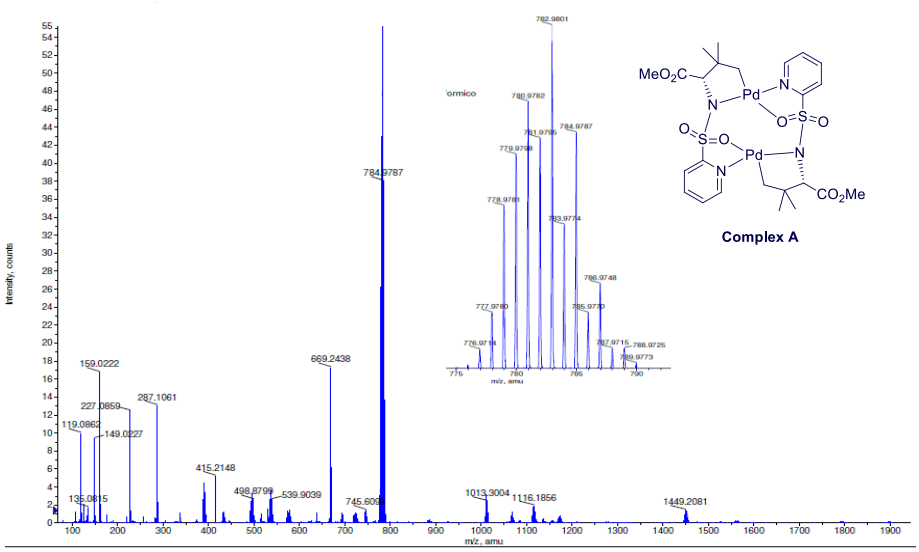
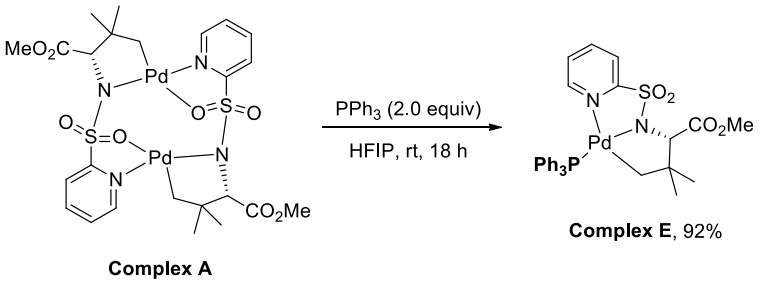


Figure 3.10: HRSM spectrum of complex A in DCM

The considerably higher reactivity displayed by **complex A** in CD_3CN compared to that in CD_2Cl_2 points towards a mechanism whereby the dinuclear **complex A** is transformed into mononuclear species such as **A´** by direct ligand substitution of the bidentate (2-pyridyl)sulfonyl ligand by the weakly coordinating CD_3CN used as solvent.

Even though the active monomeric species could not be isolated (likely due to its partial equilibration with the corresponding dinuclear species), the reaction of dimeric **complex A** with 1.0 equiv (with respect to the Pd) of a stronger ligand, such as PPh_3, in HFIP at room temperature, furnished directly the monomeric **complex E** in an excellent 92% yield (Scheme 3.84). Unfortunately, all our attempts to characterize **complex E** by single-crystal X-ray analysis were unsuccessful. However, this monomeric complex was fully characterized by NMR, as well as by mass spectroscopy.



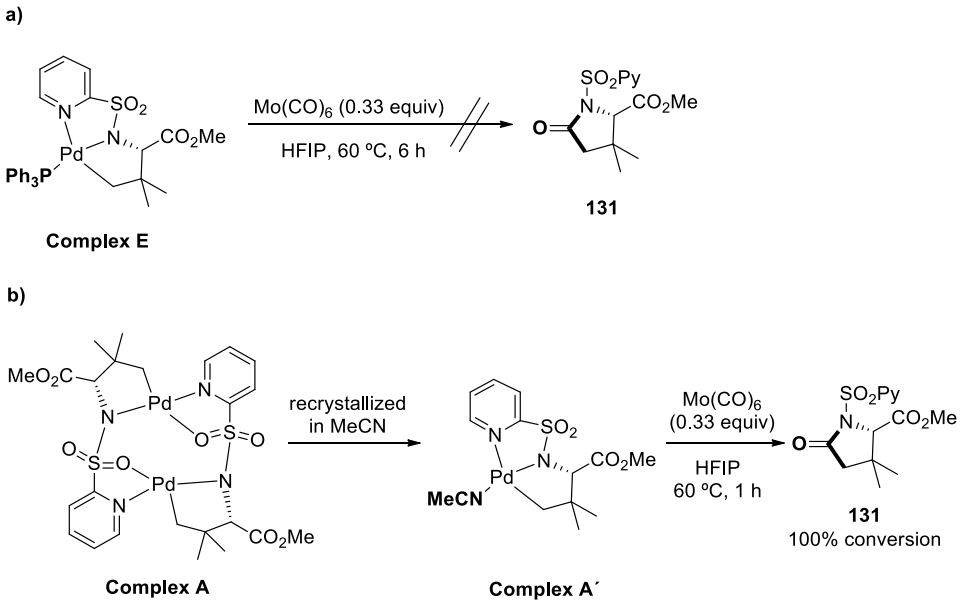
Complex A

Complex E, 92%

Scheme 3.84

The reactivity of **complex E** in the C–H carbonylation reaction was next investigated. No reaction was observed when **complex E** was allowed to react with $Mo(CO)_6$ (0.33 equiv) under the optimized reaction conditions after 6 h (Scheme 3.85a). In contrast, when **complex A** was dissolved and recrystallized in CH_3CN, and the resulting complex (presumably **A´**) was subjected to identical reaction conditions, the expected 2-prolinone **131** was quantitatively formed after just 1 h at 60 ºC (Scheme 3.85b). Because the C–H carbonylation reaction requires dissociation of

this external ligand from **complex E** (PPh_3) or from **complex A´** (MeCN), the greater lability of MeCN should facilitate ligand displacement by CO and, in turn, enhance the rate of the carbonyl insertion step.



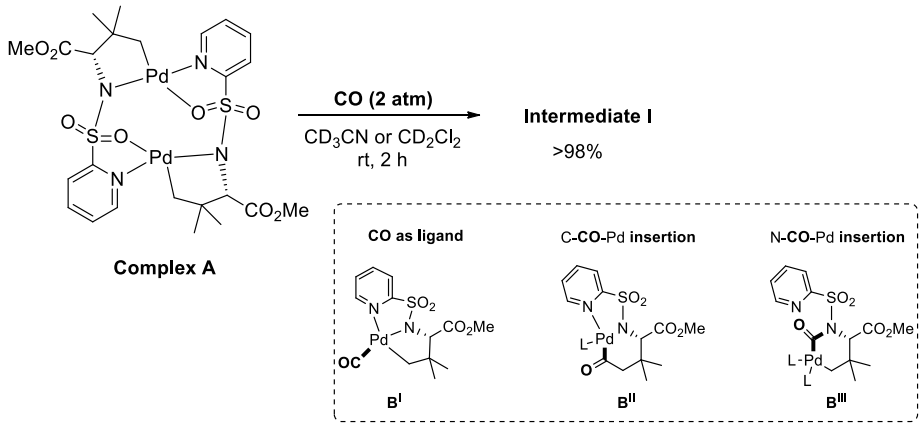
Scheme 3.85

At this point, taking into account all the above experiments, it seems reasonable to consider the monomeric species **A´** as the catalytically active species of the carbonylation reaction.

- **Structural characterization of Intermediate B**

As described earlier, the formation of **intermediate B** from bimetallic **complex A** was cleanly achieved by simple stirring in CD_3CN or CD_2Cl_2 under gaseous atmosphere of CO (2 atm) for 2 h (Scheme 3.86). Due to the above-mentioned instability of this compound, the reactions were carried out in deuterated solvents to facilitate intermediate characterization by NMR, HRMS and IR spectroscopies,

thereby avoiding unnecessary further manipulation. At this point we speculated that the **intermediate B** could be either a palladium-carbonyl complex preceding carbonyl insertion (species $\mathbf{B^{I}}$) or a palladium complex resulting from 1,1-migratory insertion of CO into the Pd–C or the Pd–N bond (species $\mathbf{B^{II}}$ or $\mathbf{B^{III}}$, respectively).



Scheme 3.86

It was found that the sample of **intermediate B** in CD_3CN was much more unstable than that in CD_2Cl_2. In CD_3CN, **intermediate B** completely reverts to **complex A´** upon 12 h at rt in the NMR tube, whereas the same **intermediate B** was found to be stable at rt in CD_2Cl_2 for 12 h. The ^{1}H NMR spectra of **intermediate B** in CD_3CN or CD_2Cl_2 were very similar to that of **complex A** in the same deuterated solvents, providing little structural information (just small differences in chemical shifts). However, the ^{13}C NMR spectrum in CD_3CN (at -20 ºC to minimize decomposition) showed two extra peaks compared to the ^{13}C NMR spectrum of **complex A**. While one of them at 179.0 ppm, was assigned to a CO bonded to the Pd center,[230] the other one, at 125.4 ppm, with a very low intensity, was tentatively

[230] This chemical shift is consistent with values previously reported for similar Pd-carbonyl complexes (160-180 ppm). For selected publications on the characterization of palladium carbonyl complexes, see: a) J. –A. García-López, M. –J. Oliva-Madrid, I. Saura-Llamas, D. Bautista, J. Vicente, *Organometallics*, **2013**, *32*, 1094. b) R. Trebbe, R. Goddard, A. Rufinska, K. Seevogel, K. –P.

assigned to the nitrile carbon of the CD_3CN ligand bonded to the Pd center in the monomeric **complex A´** which is slowly formed by decomposition of **intermediate B**, likely through CO ligand displacement by CD_3CN.[231,232]

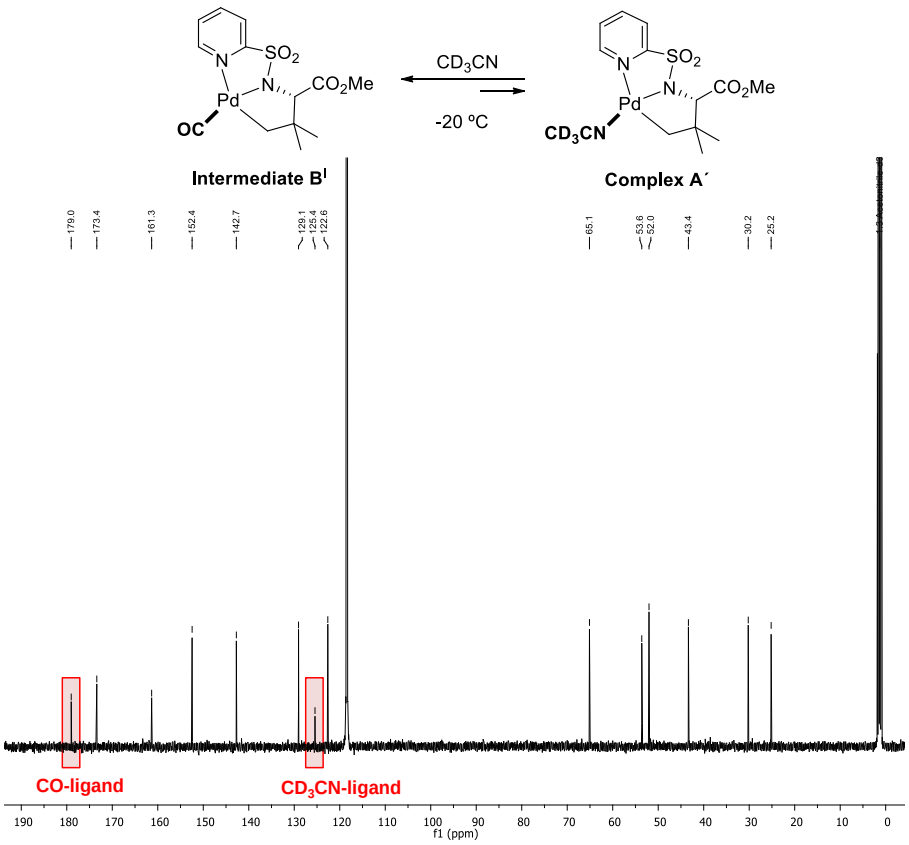


Figure 3.11: ^{13}C NMR spectrum of intermediate B in CD_3CN

Pörschke, *Organometallics*, **1999**, *18*, 2466. For a review on palladium carbonyl complexes, see: c) T. A. Stromnova, I. I. Moiseev, *Russ. Chem. Rev.* **1998**, *6*, 485. For a selected textbook for transition metal complexes syntheses, see: d) R. J. Angelici, *Reagents for Transition Metal Complex and Organometallic Syntheses*, Wiley & Sons., New York, **1990**.

[231] The CD_3 group of this CD_3CN ligand appeared overlapped with the signal of the solvent.

[232] This extra peak was not observed when the ^{13}C NMR was carried out in CD_2Cl_2.

Importantly, **intermediate B** was detected as the highest intensity peak upon analysis by ESI-HRMS of a CD_2Cl_2 solution [m/z $(M+CO+H)^+$: 418.9893] accompanied by the corresponding C–H activation **complex A´´** after loss of CO [m/z $(M-CO+H)^+$: 390.9943].[233]

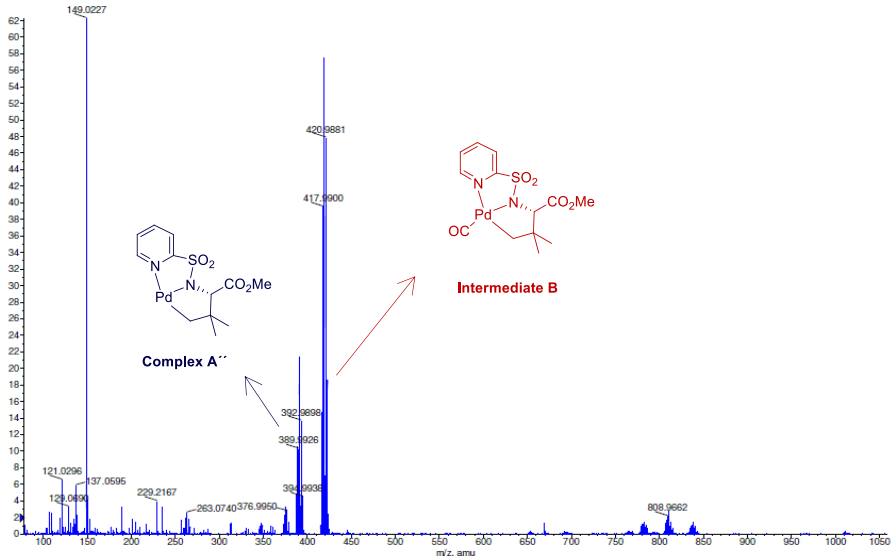


Figure 3.12: HRSM spectrum of intermediate B in CD_2Cl_2

We definitively corroborated the presence of a CO molecule as external ligand in the structure of **intermediate B**[I] by IR spectroscopy. A very representative peak at 2095 cm^{-1} (observed both in CD_3CN and CD_2Cl_2) was very characteristic and perfectly matches with previously reported data for similar palladium-carbonyl complexes (typically in the range of 1900-2100 cm^{-1}).[230] The stretch vibration corresponding to the carbonyl group of the methyl ester moiety appeared, as expected, at 1742 cm^{-1} (Figure 3.13).

[233] A very similar result was achieved in CD_3CN: **Intermediate B**; [m/z $(M+CO+Na)^+$: 440.9712] and **complex A´´;** [m/z $(M-CO+Na)^+$: 412.9762].

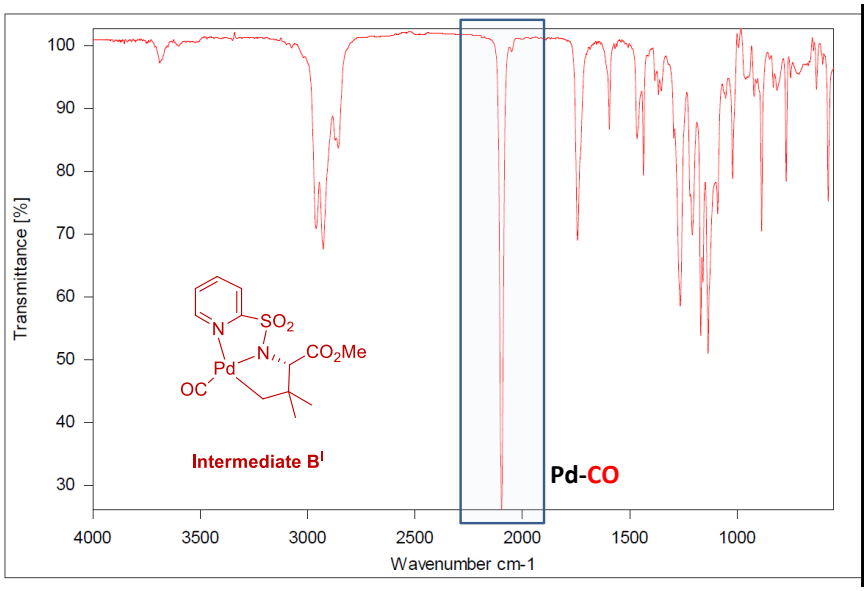


Figure 3.13

- **DOSY NMR experiments of intermediate B in CD_3CN and CD_2Cl_2**

To further support the monomeric nature of the **intermediate B**, a diffusion-ordered NMR spectroscopy (DOSY) experiment was carried out at 5 ºC in CD_3CN.[234] For this purpose, a 58:42 mixture of monomeric **complex A´** and **intermediate B** was studied (Figure 3.14). The diffusion coefficients *D* were estimated for both substrates as an average of 12 independent measurements for

[234] Diffusion-ordered spectroscopy (DOSY) seeks to separate the NMR signals of different species according to their diffusion coefficient. A series of spin echo spectra are measured with different pulsed field gradient strengths, and the signal decays are analyzed to extract a set of diffusion coefficients with which to obtain the diffusion coefficient of a DOSY spectrum. For selected textbooks see: a) A. Macchion, G. Ciancaleoni, C. Zuccaccia, D. Zuccaccia, *Diffusion Ordered NMR Spectroscopy (DOSY). Supramolecular Chemistry: From Molecules to Nanomaterials*, Wiley & Sons, Chichester, **2012**. b) G. A. Morris, R. K. Harris, R. E. Wasylishen, *Diffusion-Ordered Spectroscopy*, Wiley & Sons, Chichester, **2009**. For a review on diffusion NMR spectroscopy, see: c) Y. Cohem, L. Avram, L. Frish, *Angew. Chem. Int. Ed.* **2005**, *4*, 520.

each peak. A theoretical molecular weight (MW_c) was calculated from the obtained diffusion coefficients applying the model proposed by Morris and the excel spreadsheet provided by the authors [**intermediate B**; 350.80 g/mol and **complex A´**; 443.20 g/mol].[235] Additionally, as small molecules can be considered as independent spheres in the media, their hydrodynamic radii were estimated by the Stokes-Einstein equation.[236] The hydrodynamic radii estimated for monomeric **complex A´** and **intermediate B**, presented similar values (4,45 Å and 4.00 Å, respectively), which is in accordance with the expected monomeric nature of both structures (Figure 3.15).

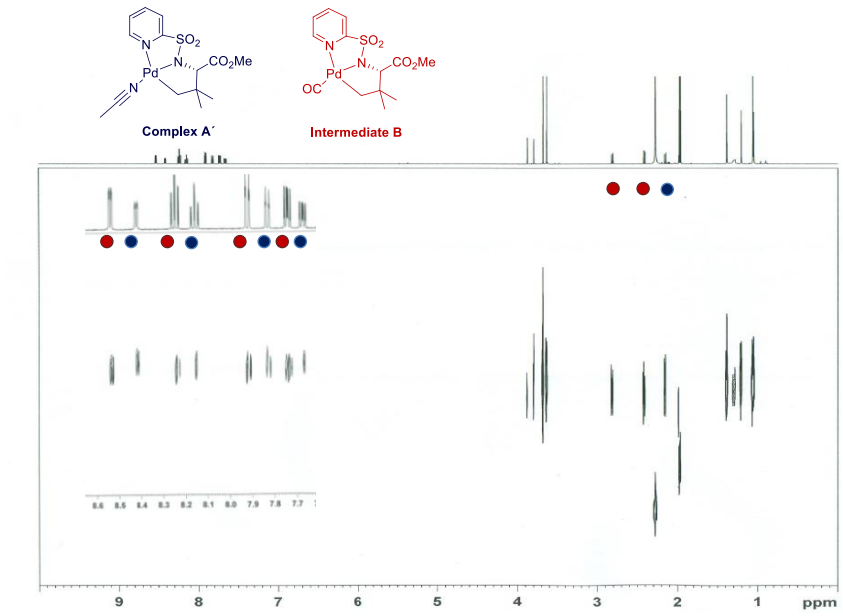


Figure 3.14

[235] a) R. Evans, Z. Deng, A. K. Rogerson, A. S. McLachlan, J. F. Richards, M. Nilsson, G. A. Morris, *Angew. Chem. Int. Ed.* **2013**, *52*, 3199.

[236] $D = \frac{Kb\,T}{6\pi\,\eta o\,R}$; where D is the diffusion coefficient ($m^2.s^{-1}$); K_b the Boltzmann constant 1.38065 x 10^{-23} ($J.K^{-1}$); T the temperature (K); η_o the viscosity ($Kg.m^{-1}.s^{-1}$) and R the radius (m). The values employed for CD_3CN at 278 K were found at the online Dortmund Data Bank: density ρ = 0.7978 $g.mL^{-1}$; viscosity η_o = 0,419 x 10^{-3} $Kg.m^{-1}.s^{-1}$; MW = 44,0704 $g.mol^{-1}$.

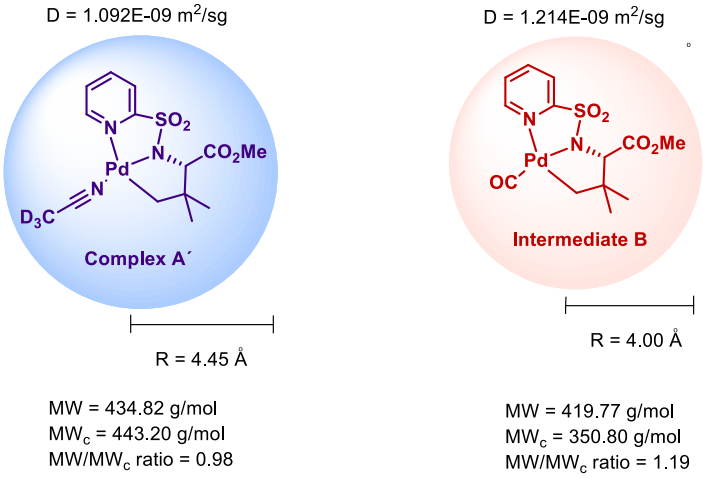


Figure 3.15

Given the fact that in CD_2Cl_2 the predominant species in solution for **complex A** is a dimeric Pd-complex, which is expected to presents a larger hydrodynamic radio, we performed a similar DOSY experiment of a 40:60 mixture of **complex A** and **intermediate B** in CD_2Cl_2 at rt (Figure 3.16).[237] As expected, the calculated hydrodynamic radio for **complex A** (5.52 Å) not only was significantly higher than that observed for **intermediate B** (4.11 Å), but also greater that the estimated value for monomeric **complex A´** in CD_3CN (4.45 Å). On the other hand, similar values of hydrodynamic radii were estimated for **intermediate B** in CD_3CN (4.00 Å) and CD_2Cl_2 (4.11 Å) (Figure 3.17).

[237] The values employed for CD_2Cl_2 at 298 K were found at the online Dortmund Data Bank: density ρ = 1.3620 g.mL^{-1}; viscosity η_o = 0,420 x 10^{-3} Kg.m^{-1}.s^{-1}; MW = 86.9403 g.mol^{-1}.

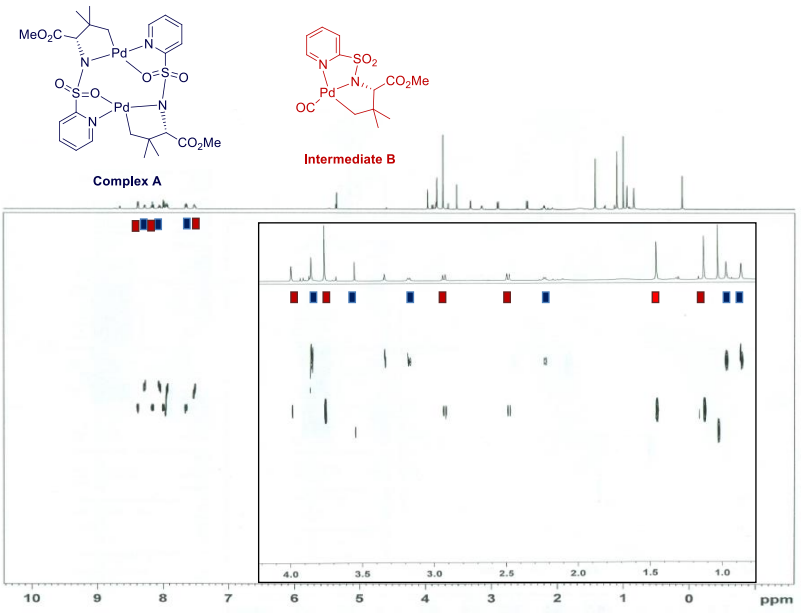


Figure 3.16

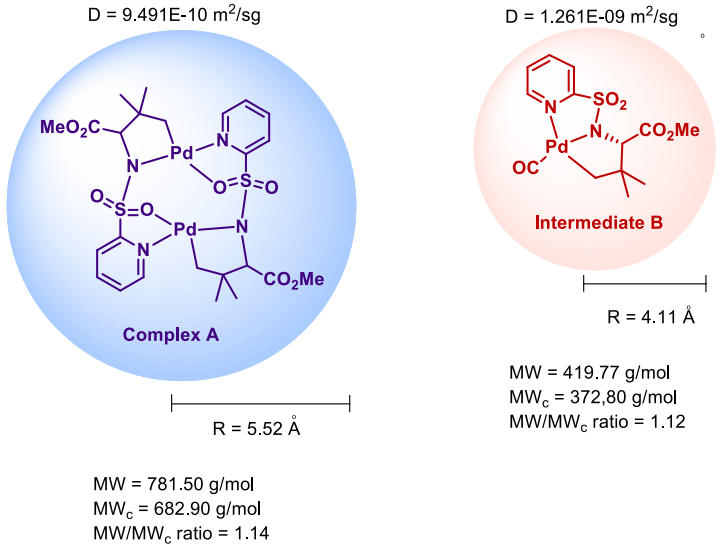


Figure 3.17

- **Computational studies**[238]

To deeply understand our carbonylation/cyclization reaction mechanism a complete energy profile for the reaction of the *N*-(2-pyridyl)sulfonyl *tert*-leucine derivative **130** in the gas phase was calculated (Figure 3.18).[239] Among the several potential mechanisms by which the C–H activation step may occur, a concertated metallation-deprotonation (CDM) pathway has often been found to be the most favourable.[240] The most stable transition state found for this C–H activation was **TS(Ib-IIb)** in which the six-membered cycle formed by Pd, N and the rest of the amino acid moiety, including the C–H bond being cleaved, adopts a distorted chair-like conformation.[241] After the C–H activation process, a bicyclic five-five-membered palladium intermediate is formed [**IIb**, 5.8 (1.9) kcal/mol] which could suffer a ligand exchange between the acetic acid and an acetonitrile solvent molecule, thus generating intermediate **IIIb** [-1.2(-7.1) kcal/mol] as a stable palladium(II) complex stabilized by the pyridine ring and the acetonitrile molecule. In the presence of CO ligands, another ligand exchange can take place between the labile acetonitrile and the CO ligand, generating an even more stable intermediate **IVb** [-10.2(-15.4) kcal/mol] in which the sulfonamide nitrogen and the CO presents a *trans*-conformation. Due to the acetonitrile, the pyridine ring can be displaced achieving two possible intermediates that are stabilized by a solvent molecule and the CO where the pyridine ring lies out of the plane, **Vb** and **V´b** [-9.1(-8.4) and -1.3(-5.5) kcal/mol, respectively]. While in **V´b** the sulfonamide nitrogen and the CO

[238] These computational studies have been performed by Dr. Inés Alonso ("Profesora titular", member of our research group).

[239] [M06/6-311 + G(2df, 2p) (C, H, N, O, S), SDD (Pd)//B3LYP/6-31G(d) (C, H, N, O, S), SDD (Pd)]. Relative G values are reported at 298 K (kcal/mol). Additionally, single point solvation energy corrections (CH_3CN, CPCM model) are indicated in parentheses.

[240] a) I. A. Sanhueza, A. M. Wagner, M. S. Sanford, F. Schoenebeck, *Chem. Sci.* **2013**, *4*, 2767. b) D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echevarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880. c) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848.

[241] A similar combination of DFT methods and basis set have been used to study C-H activation processes involving mono, bi or trinuclear Pd^{II} complexes, see: R. Giri, Y. Lan, P. Liu, K. N. Houk, Jin-Q. Yu, *J. Am. Chem. Soc.* 2012, **134**, 14118.

ligand presents a *cis*-configuration, in **Vb** both ligands are in *trans*-arrangement. The CO insertion just could be achieved from **Vb** *via* a high energetic transition state **TS(Vb-VIb)** [19.1(16.4) kcal/mol] where a penta-coordinated palladium structure is proposed. In this transition state, the Pd–C bond is being cleaved while the C–CO–Pd bond is being formed (insertion) by a three membered-ring in a concertated way, yielding **VIb** as a bicyclic six-five-membered palladium(II) intermediate in which the other vacancies are occupied by an acetonitrile ligand and the pyridine ring. All the attempts to find a similar transition state from **V´b** failed, probably due to an important electronic repulsion between CO and SO_2 groups. These results finally suggest that the CO insertion probably take place *via* the ketone intermediate (C–CO–Pd), dismissing other alternative hypothesis which proceeded *via* the CO insertion on the sulfonamide N–Pd bond (amide intermediate, N–CO–Pd). Intermediate **VIb** evolves through a reductive elimination transition state where the N–CO bond is being formed as the Pd–CO bond is being cleaved, **TS(VIb-VIIb)** [10.4(6.9) kcal/mol)] yielding the cyclized intermediate **VIIb** [-10.2(-14.3) kcal/mol)] where the ester moiety adopts a pseudoecuatorial conformation. However, a more stabilized intermediate was proposed were the ester group presents a pseudoaxial conformation, **VIIIb** [-13.4(-17.7) kcal/mol)].

This energy profile also suggests that both the C–H activation and the CO insertion transition states present similar energy values: 19.7 and 19.1 kcal/mol, respectively, and thus both could act as reaction limiting steps (having the C–H activation step a slightly higher energy barrier).

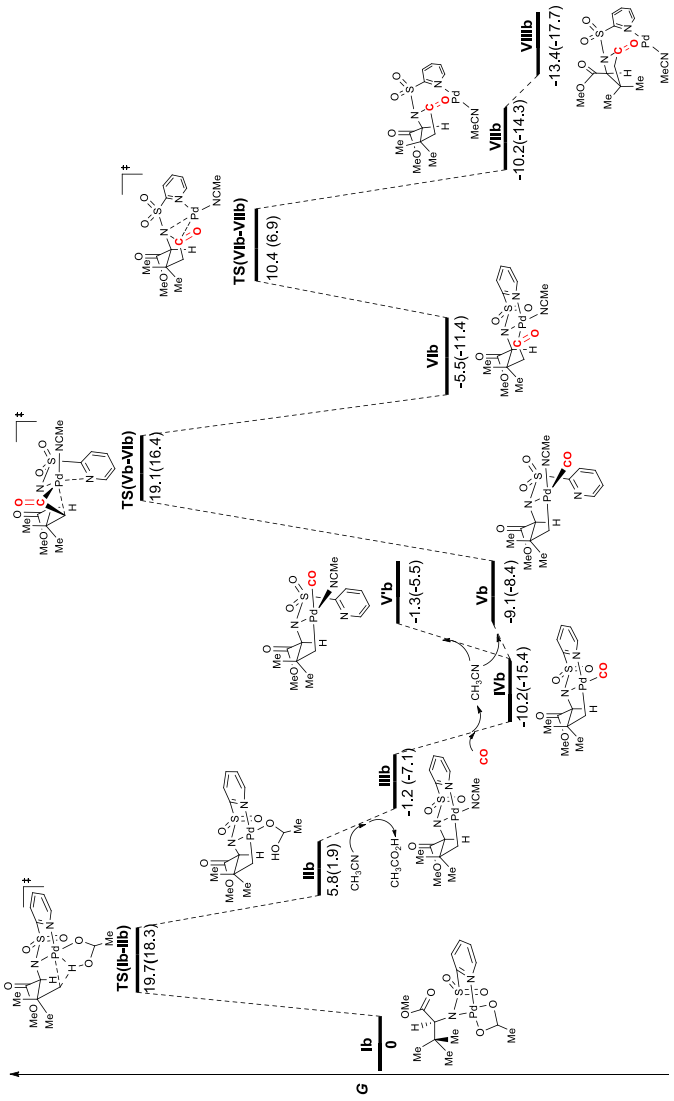
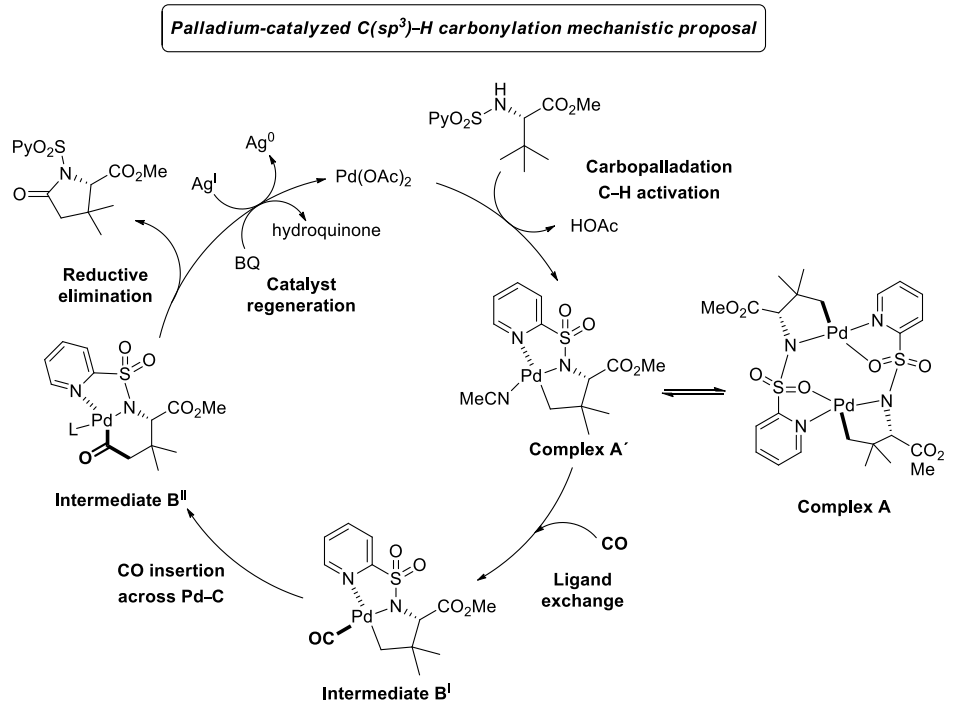


Figure 3.17[242]

[242] [M06/6-311 + G(2df, 2p) (C, H, N, O, S), SDD (Pd)//B3LYP/6-31G(d) (C, H, N, O, S), SDD (Pd)]. Relative G values are reported at 298 K (kcal/mol). Additionally, single point solvation energy corrections (CH_3CN, CPCM model) are indicated in parentheses.

On the basis of these mechanistic insights gained from both experimental and theoretical studies, we propose the catalytic cycle presented in Scheme 3.87. We reasoned that the reaction might proceed through initial Pd^{II}-catalyzed γ-C–H activation *via* a concertated metallation-deprotonation (CMD) mechanism assisted by the acetate ion, thus leading to the bimetallic **complex A**, which is in equilibrium with an active monomeric **complex A´**. The latter might undergo solvent ligand displacement by CO to afford **intermediate B^{I}**. Carbonyl insertion across the Pd–C bond (**intermediate B^{II}**, energetically favoured over the insertion across the Pd–N bond), followed by reductive elimination yields the carbonylative cyclization product. The so formed reduced Pd^{0} species is then reoxidized back to the active Pd^{II} species *via* the combined action of BQ and AgOAc.[243]

[243] For the catalytic cycle, the role of AgOAc is not entirely clear. Since, in the stoichiometric reaction, the formation of **complex A** and its reaction with $Mo(CO)_6$ take place without AgOAc, providing cleanly the carbonylation product **131**, we might intuitively rule out that AgOAc is necessary for the C–H activation step to take place. Instead, the Ag salt is likely acting as an oxidant for the palladium center. Moreover, silver salts could also be involved in the formation of hetero-bimetallic Pd-Ag species, which could participate in the C–H activation step. See: a) Y. –F. Yang, G. –J. Cheng, P. Liu, D. Leow, T. –Y. Sum, P. Chen, X. Zhang, Y. –Q. Yu, Y. –D. Wu, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 344. b) M. Anand, R. B. Sunoj, H. F. Schaefer III, *J. Am. Chem. Soc.* **2014**, *136*, 5535.

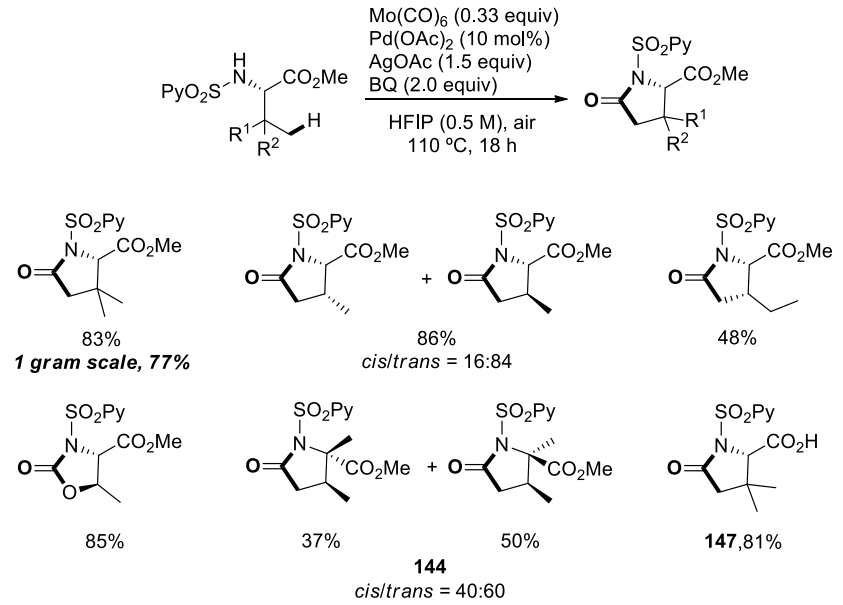

Palladium-catalyzed C(sp3)–H carbonylation mechanistic proposal
Carbopalladation
C–H activation
HOAc
Pd(OAc)2
Ag0
AgI
hydroquinone
BQ
Catalyst
regeneration
Reductive
elimination
Complex A´
Complex A
Ligand
exchange
CO
CO insertion
across Pd–C
Intermediate BII
Intermediate BI
MeCN

Scheme 3.87

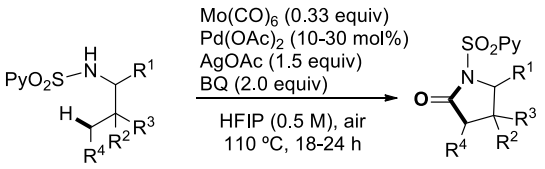
3.8. Conclusions

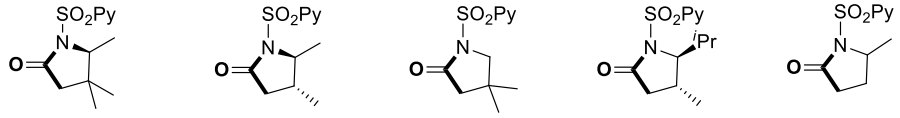
In summary, we have developed a practical and reliable Pd-catalyzed procedure for the site-selective γ-C(sp^3)–H carbonylation/cyclization of aliphatic amine derivatives, including α-amino acids and peptides, thus leading to the corresponding γ-lactams in good yields through a twofold carbonylation [at both C(γ)–H and N–H bonds]. This new protocol strongly relies on the excellent directing ability displayed by the *N*-(2-pyridyl)sulfonyl protecting group, which also proved to be easily removed under smooth conditions. Importantly, the use of a substoichiometric amount of $Mo(CO)_6$ (0.33 equiv) as the source of CO not only avoids the difficulties in handling toxic gaseous carbon monoxide, but also enables slow *in situ* generation of CO, thus preventing catalyst deactivation under an excess of CO by competitively occupying coordination sites on the Pd^{II} center. The advances accomplished in this project, in a more detailed fashion, are listed below:

1) A number of *N*-(2-pyridyl)sulfonyl-protected α-amino acid derivatives undergo smooth carbonylative cyclization under the optimized conditions to afford the corresponding 5-oxoproline derivatives in synthetically useful yields with no loss of enantiopurity when starting from optically pure substrates. The reaction did tolerate the presence of a free carboxylic acid group (product **147**) and enabled the formation of 5-oxoprolines with a stereogenic tetrasubstituted carbon at C2 (product **144**). Substrates having two diastereotopic β-methyl groups yielded the corresponding product as a mixture of *cis*/*trans* diastereoisomers with moderate stereoselectivity in favour of the *trans*-derivative.



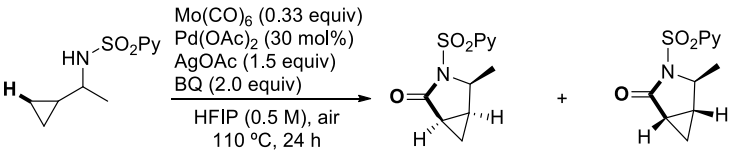
2) This carbonylation protocol could also be extended to other substrates such as simple aliphatic amines. A range of *N*-(2-pyridyl)sulfonyl-protected amines afforded the corresponding γ-lactams in good to excellent yields and moderate to excellent diastereoisomeric ratios (50-92% yield, *cis*/*trans* = 50:50-<2:>98). It is also remarkable the desymmetrization of 2,4-dimethylpetan-3-amine (bearing two *iso*-propyl groups at the α-position), affording the corresponding pyrrolidone derivative in 71% yield with a total *trans*-diastereocontrol (**160**). A structural limitation encountered is that branching at the β-position with respect to the nitrogen seems to be an essential biasing element for the reaction to take place.





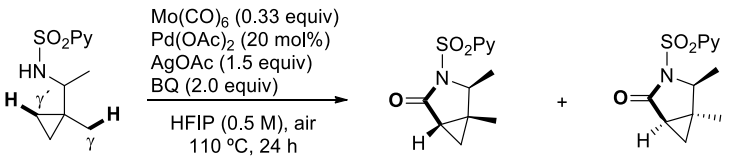
89% **1.0 gram scale, 85%** | 78% *cis*/*trans* = 23:77 | 71% | 71% *cis*/*trans* = <2:>98 | 0%

3) The reaction also proved to be effective for the activation of γ-methylene C–H bonds of cyclopropanes and norbornane substituents. It is interesting that a cyclopropyl-γ-C(sp^3)–H bond can be selectively carbonylated over a methyl γ-C(sp^3)–H bond.



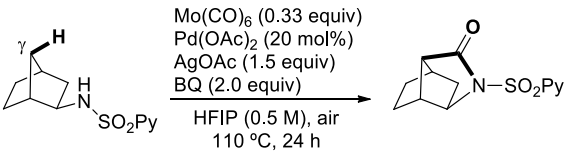
161 → *cis*-**163** + *trans*-**163**

60%
cis/*trans* = 50:50



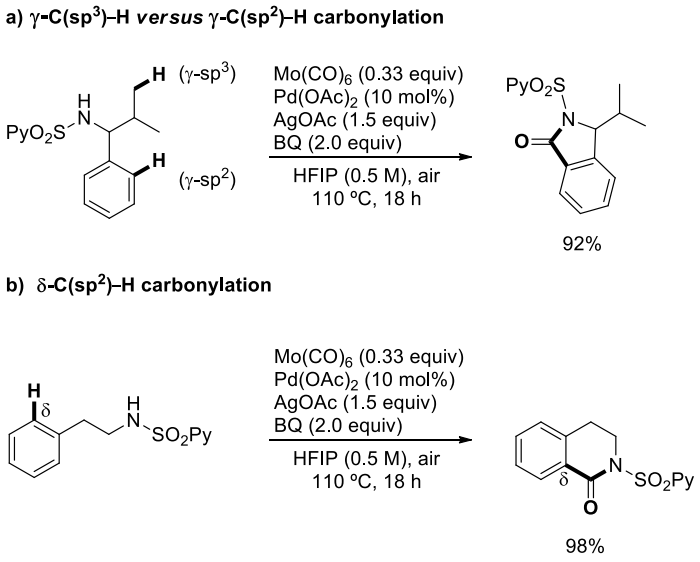
162 → *cis*-**164**, 37% + *trans*-**164**, 36%

cis/*trans* = 40:60



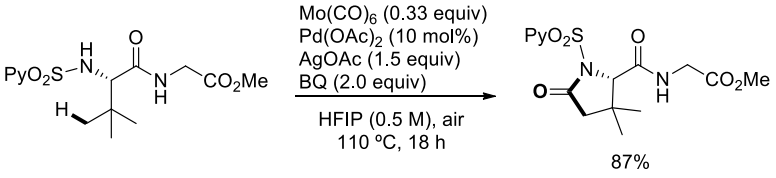
165 → **167**, 50%

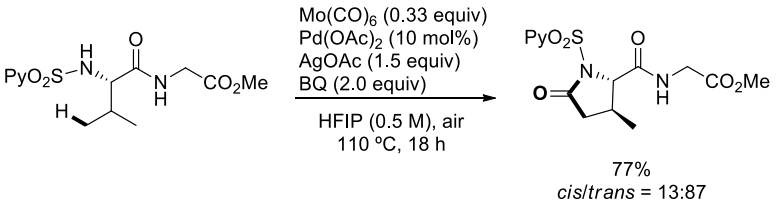
4) This procedure was selective towards the C(sp^2)–H carbonylation of amine derivatives having both C(sp^2)–H and C(sp^3)–H bonds at the γ-position. Moreover, this protocol could be extended for the δ-C(sp^2)–H carbonylation.



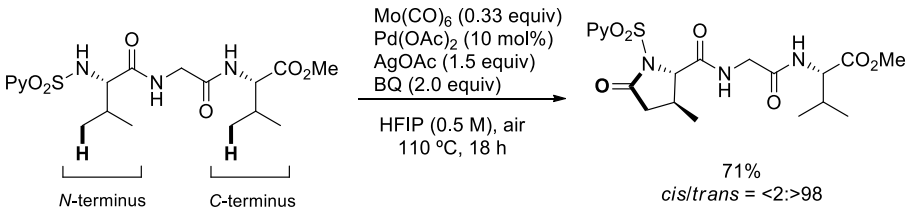
5) Importantly, this carbonylation protocol was successfully applied to the late-stage modification of relatively complex peptides (di- and tripeptides), which are much more challenging substrates because of the potential formation of competing *N*,*N*- or *N*,*O*-bis-coordinated Pd^{II} complexes. These results illustrate not only the functional group tolerance of our method, but also the capacity of the bidentate *N*-SO_2Py directing group to override other inherent substrate coordinating elements such as peptide bonds.

a) Dipeptides

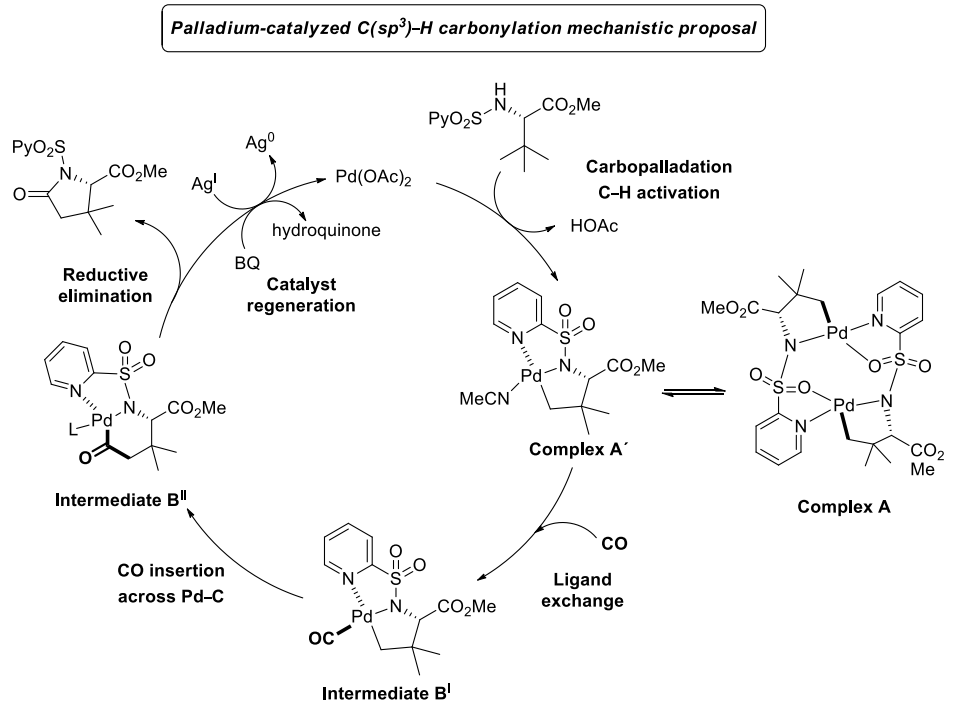




b) Tripeptides



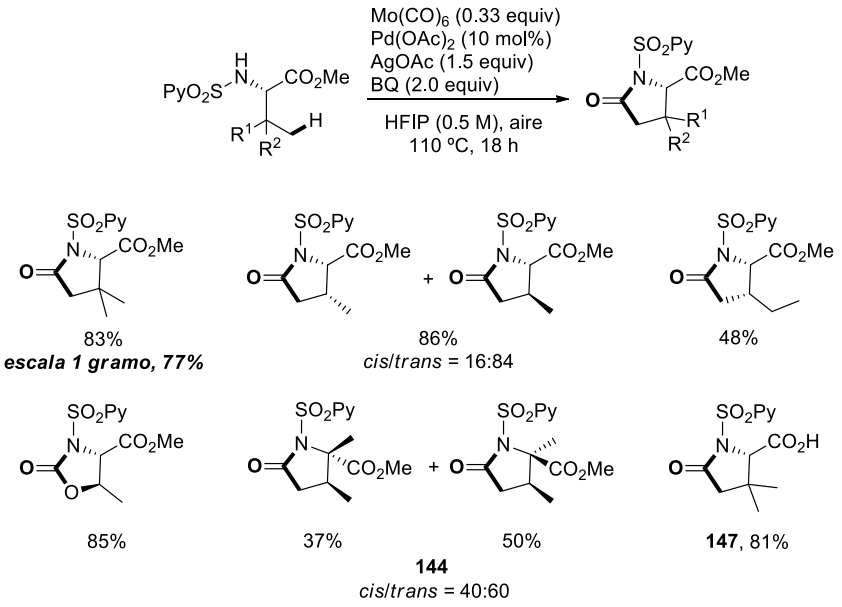
6) Mechanistic insights gained from both experimental and theoretical studies suggest that in solution, the bimetallic palladium(II) **complex A** is in equilibrium with an active monomeric species **A´**, which undergoes solvent ligand displacement by CO to afford **intermediate B^{I}**. Carbonyl insertion across the Pd–C bond (**intermediate B^{II}**, energetically favoured over insertion across the Pd–N bond), followed by reductive elimination yields the carbonylative cyclization products. The reduced palladium(0) species is then oxidized back to the active palladium(II) species *via* the combination of BQ and AgOAc.


Palladium-catalyzed C(sp3)–H carbonylation mechanistic proposal
Carbopalladation
C–H activation
HOAc
Pd(OAc)2
hydroquinone
BQ
Ag0
AgI
Catalyst
regeneration
Reductive
elimination
Complex A´
Complex A
Ligand
exchange
CO
CO insertion
across Pd–C
Intermediate BII
Intermediate BI

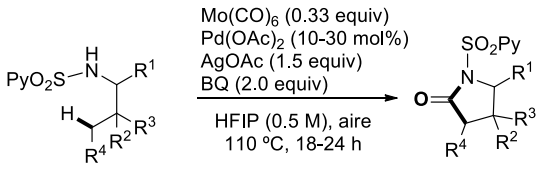
3.8. Conclusiones

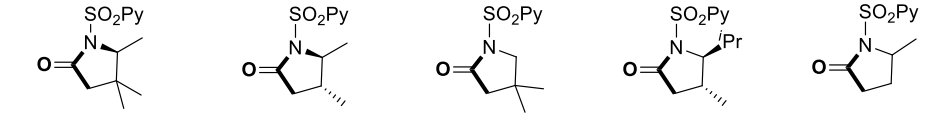
En resumen, se ha desarrollado una nueva metodología para la ciclación carbonilativa γ-C(sp^3)–H de derivados de aminas alifáticas, incluyendo α-amino ácidos y péptidos. Esta transformación permite el acceso directo a las correspondientes γ-lactamas con buenos rendimientos. El éxito de este nuevo protocolo se basa en la capacidad coordinante del grupo *N*-(2-piridil)sufonilo el cual puede ser eliminado bajo condiciones suaves de reacción. Cabe destacar el uso subestequiométrico de $Mo(CO)_6$ (0.33 equiv) como fuente alternativa de CO lo cual evita el empleo de CO gas (altamente tóxico). Además, la lenta generación de CO en el medio de reacción mantiene activo el catalizador de Pd^{II} (un exceso de CO desactiva dicho catalizador debido a la coordinación de ligandos CO con las vacantes de coordinación del metal). A continuación se explican de manera más detallada los logros conseguidos en el desarrollo de esta nueva metodología:

1) Este protocolo resultó ser compatible con un gran número de derivados de α-amino ácidos lo cual permitió el acceso directo a las correspondientes 5-oxoprolinas con buenos rendimientos. Además, cuando se utilizaron sustratos de partida enantioméricamente puros no se observó racemización en los productos finales. Cabe destacar la compatibilidad del método con un ácido carboxílico libre (producto **147**) y la formación de 5-oxoprolinas tetrasustituidas en el carbono C2 (producto **144**). Aunque cuando la posición β- se encuentra sustituida por dos metilos diastereotópicos se obtuvieron mezclas de diastereoisómeros *cis*/*trans*, el método presentó un mayor *trans*-diastereoselectividad.



2) Esta metodología también fue aplicada a otro tipo de sustratos como por ejemplo aminas alifáticas simples. Las correspondientes γ-lactamas fueron sintetizadas con buenos rendimientos y moderada diastereoselectividad (50-92%, *cis*/*trans* = 50:50-<2:>98). Cabe destacar la desimetrización de la 2,4-dimetilpenta-3-amina, la cual presenta dos grupos *iso*-propilo en la posición α, obteniéndose el correspondiente derivado ciclado con un rendimiento del 71% y una completa *trans*-diastereoselectividad. Una limitación estructural encontrada en el estudio del alcance estructural de la reacción fue la necesidad de utilizar sustratos de partida β-sustituidos.





89%
escala 1 gramo, 85%

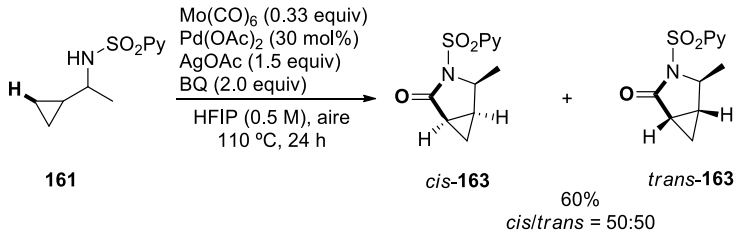
78%
cis/*trans* = 23:77

160, 71%

71%
cis/*trans* = <2:>98

0%

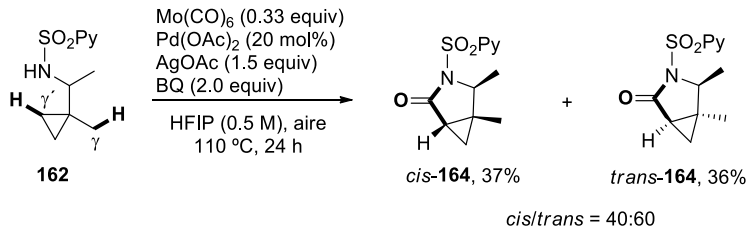
3) La reacción también resultó ser eficaz en la activación de enlaces γ-metilénicos en derivados de ciclopropano y norbornano. Es interesante destacar que la reacción de carbonilación es selectiva a enlaces γ-C(sp^3)–H secundarios frente a enlaces γ-C(sp^3)–H primarios en los derivados de ciclopropano.



161

cis-**163** + *trans*-**163**

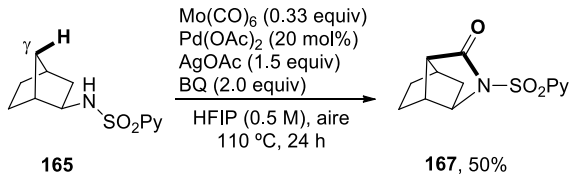
60%
cis/*trans* = 50:50



162

cis-**164**, 37% + *trans*-**164**, 36%

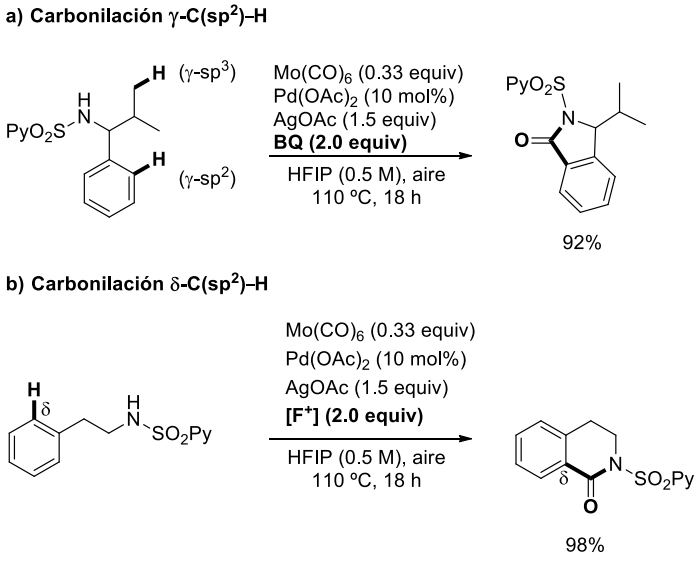
cis/*trans* = 40:60



165

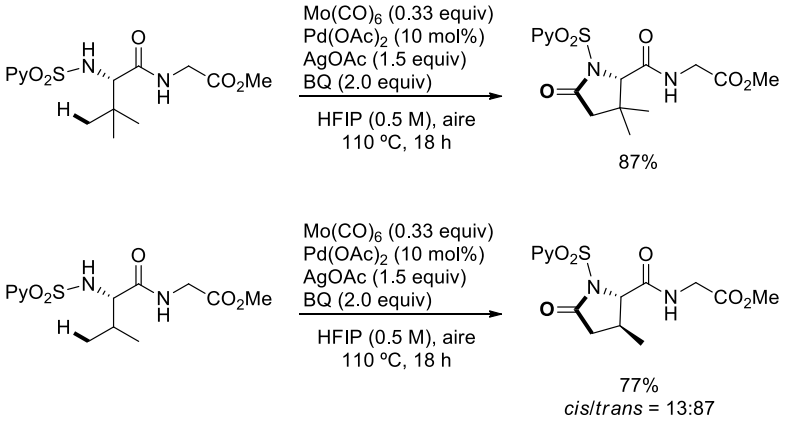
167, 50%

4) La carbonilación de enlaces γ-C(sp^2)–H fue selectiva en aquellos sustratos que presentan tanto enlaces C(sp^2)–H como enlaces C(sp^3)–H en la posición γ. Además, este protocolo permitió llevar a cabo una funcionalización δ-C(sp^2)–H en el derivado de la fenetilamina.

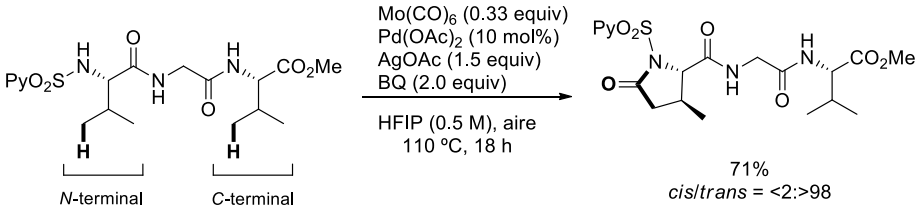


5) El gran potencial sintético de este nuevo método pudo ser aplicado a sustratos más complejos como en el caso de di- y tripéptidos. Estos sustratos, altamente funcionalizados, podrían presentar otros modos de coordinación competitivos con el Pd^{II} (del tipo *N*,*N*- o *N*,*O*). Estos excelentes resultados no sólo destacan la gran tolerancia funcional de nuestro protocolo, sino que también demuestran que la coordinación bidentada otorgada por el grupo *N*-SO$_2$Py es superior frente a otros tipos de coordinaciones inherentes a la estructura de los sustratos de partida.

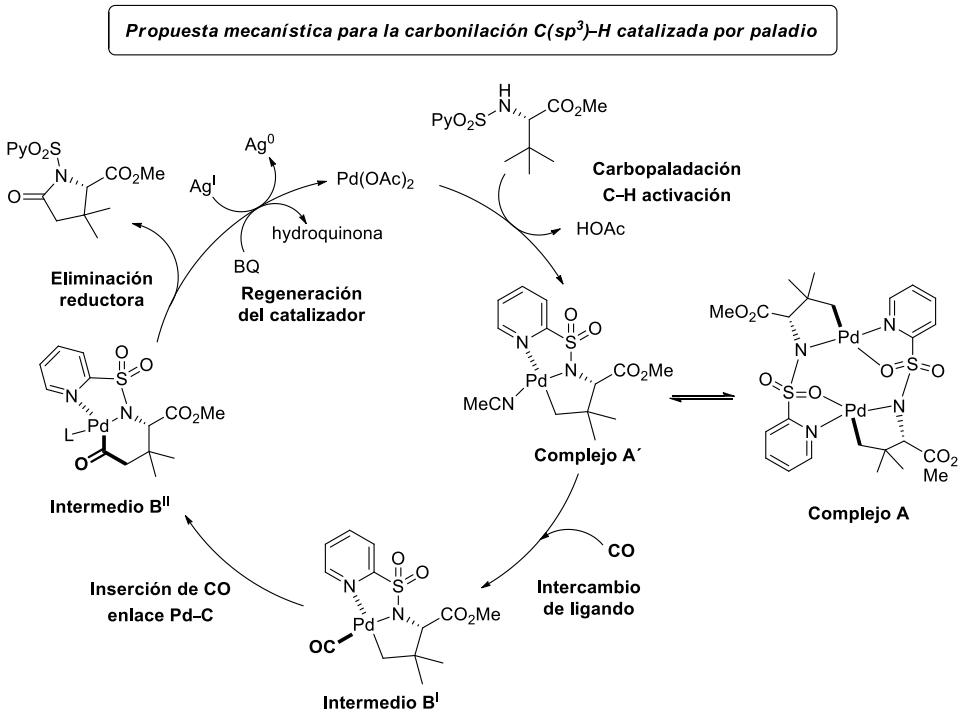
a) Dipéptidos



b) Tripéptidos



6) Estudios mecanísticos, tanto experimentales como teóricos, sugieren que en disolución, el complejo bimetálico de paladio(II) (**complejo A**) presenta un equilibrio con su forma monomérica (**complejo A´**, especie catalíticamente activa), la cual mediante un intercambio de ligando con el CO, genera el **intermedio B^{I}**. La inserción carbonilativa a través del enlace Pd–C (**intermedio B^{II}**, energéticamente favorecida sobre la inserción en el enlace Pd–N) genera, tras una eliminación reductora, los correspondientes derivados de carbociclación. La especie reducida de paladio(0) es reoxidada a su forma catalíticamente activa [paladio(II)] mediante la acción conjunta de la BQ y el AgOAc.


Propuesta mecanística para la carbonilación C(sp3)–H catalizada por paladio
Carbopaladación
C–H activación
HOAc
Pd(OAc)2
Ag0
AgI
hydroquinona
BQ
Regeneración
del catalizador
Eliminación
reductora
Complejo A´
Complejo A
Intermedio BII
Intermedio BI
CO
Intercambio
de ligando
Inserción de CO
enlace Pd–C
MeCN

.

Chapter 4:

Experimental section

4. Experimental section

4.1. General Methods

All the reactions were carried out in anhydrous solvents (PureSolv MD system) and under inert atmosphere (N_2 or Ar). The reactions were followed by thin layer chromatography, silica gel Merck-60 (0.25 mm) and the desired compounds were purified by flash column chromatography, Merck-60 (230-400 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were recorded at room temperature [*Bruker AV-300*, *AVII-300* and *AVIII-HD-300* (300 and 75 MHz, respectively) or *Bruker DRX-500* (500 and 125 MHz, respectively), indicated in each case]. Chemical shifts (δ, ppm) were calibrated with respect to the solvent peak: Acetone-d_6 (2.06 and 29.8 ppm), $CDCl_3$ (7.26 and 77.0 ppm); CD_3OD (3.31 and 49.0 ppm), C_6D_6 (7.16 and 128.0 ppm), D_2O (4.80 ppm), DMSO (2.5 and 39.5 ppm). Mass spectra (HRMS) were determined by: ESI (*ABSciex QSTAR pulsar*), MALDI TOF (*Bruker Daltonics Ultraflex III*), EI (*Waters GC-TOF*), FAB (*Waters VG Autospect*). Elemental analysis were measured in a *Perkin-Elmer serie II 2400 CHN* and IR spectra were recorded on a *Bruker IFS 66V* apparatus. Optical rotations were measured on a *Perkin-Elmer 241MC* polarimeter using a 10 cm cell with the solvent and concentration stated, at 589 nm sodium lamp. HPLC experiments were conducted using Daicel Chiralpak AD and IA columns (^{i}PrOH/Hexane) or (MeOH/CO_2) on an *Agilent 1100 HPLC Aurora SFC Systems* with an *Agilent 1290 Infinity Valve Driver*. Melting points were taken in open-end capillary tubes in a *Büchi Melting Point B-540* apparatus.

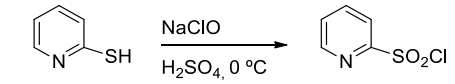
4.2. Copper-catalyzed mild nitration of protected anilines

All general reagents were obtained from usual commercial sources and were used, except when noted, without further purification. Copper nitrate hydrate (99.999%), and nitric acid metal free (70% w/w, purity >99.999% trace metals basis) were purchased from Aldrich Chemical Co. The O_2 was supplied with a purity of 99.99%.

4.2.1. Synthesis of *N*-protected anilines

- ***Synthesis of N-(2-pyridyl)sulfonyl aniline derivatives***

➢ ***Synthesis of (*2-pyridyl)sulfonyl chloride**

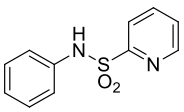


2-mercaptopyridine (2-pyridyl)sulfonyl chloride

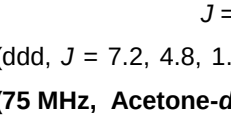
To a solution of 2-mercaptopyridine (4.0 g, 36.0 mmol) in conc. H_2SO_4 (100 mL) was added dropwise a commercially available bleach solution (roughly 5% NaOCl, 400 mL). The resulting mixture was stirred at 0 ºC for 15 min before it was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phase was dried (Na_2SO_4) and concentrated (*caution: in a fume hood because of the presence of Cl_2*) to afford the (2-pyridyl)sulfonyl chloride as a colorless oil. This compound is relatively unstable at room temperature and it was immediately used without further purification. **^{1}H NMR** δ (ppm): 8.85 (d, *J* = 4.6 Hz, 1H), 8.14 (d, *J* = 7.5 Hz, 1H), 8.07 (tt, *J* = 7.5, 1.3 Hz), 7.72 (ddd, *J* = 7.5, 4.6, 1.2 Hz, 1H).

➢ ***Typical procedure A*:** To a solution of aniline (4.00 mmol, 1.00 equiv) in THF (40 mL), pyridine (388 µL, 4.80 mmol, 1.20 equiv) and (2-pyridyl)sulfonyl chloride (852 mg, 4.80 mmol, 1.20 equiv) were successively added dropwise at 0 ºC and under N_2 atmosphere. The mixture was warmed up to room temperature and stirred overnight. During this time, a gradual formation of a precipitate was observed. The resulting mixture was then filtered off into a round-bottomed flask, and the filter cake was washed with THF (3 x 10 mL). To the resulting filtrate and washes, water (20 mL) was added and the THF was removed by evaporation at reduced pressure, yielding a suspension of a white solid in the aqueous medium. This solid was collected by filtration, washed sequentially with toluene (2 x 5 mL) and diethyl ether (2 x 5 mL). Then it was transferred to a round-bottomed flask, and dried to provide the desired compound.

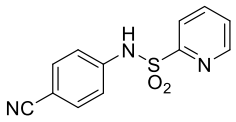
***N*-Phenylpyridine-2-sulfonamide (1).** Compound **1** was prepared following the typical procedure A from aniline (364 µL, 4.00 mmol) to give **1** as a white solid; yield: 862 mg (92%); mp = 170-172 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.19 (bs, 1H, N*H*), 8.69 (dd, *J* = 3.6, 1.2, 1H), 8.06 – 7.98 (m, 1H), 7.98 – 7.91 (m, 1H), 7.59 (ddd, *J* = 7.2, 4.8, 1.5, 1H), 7.33 – 7.14 (m, 4H), 7.03 (t, *J* = 7.2 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 157.8, 150.9, 139.0, 138.5, 129.8, 127.9, 125.2, 123.4, 121.8. **HRMS-ESI** calcd. for $C_{11}H_{11}N_2O_2S$ $(M+H)^+$: 235.0535; Found: 235.0537.



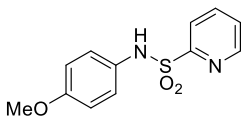
***N*-(*p*-Tolyl)pyridine-2-sulfonamide (3).** Compound **3** was prepared following the typical procedure A from *p*-toluidine (440 µL, 4.00 mmol) to give **3** as a white solid; yield: 934 mg (94%); mp = 196-197 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.04 (bs, 1H, N*H*), 8.69 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (td, *J* = 7.7, 1.7 Hz, 1H), 7.92 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.58 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.08 – 6.98 (m, 2H), 2.20 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 158.1, 150.9, 139.0, 135.9, 135.0, 130.3, 127.8, 123.5, 122.6, 20.7. **HRMS-ESI** calcd. for $C_{12}H_{13}N_2O_2S$ $(M+H)^+$: 249.0692; Found: 249.0691.



***N*-(4-Cyanophenyl)pyridine-2-sulfonamide (21).** Compound **21** was prepared following the typical procedure A from 4-aminobenzonitrile (473 mg, 4.00 mmol) to give **21** as a white solid; yield: 842 mg (81%); mp = 240-241 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.83 (bs, 1H, N*H*), 8.69 (dt, *J* = 4.7, 1.2 Hz, 1H), 8.11 (t, *J* = 1.4 Hz, 1H), 8.09 (d, *J* = 1.3 Hz, 1H), 7.77 – 7.54 (m, 3H), 7.56 – 7.43 (m, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 157.6, 151.2, 143.3, 139.5, 134.2, 128.4, 123.5, 120.3, 119.1, 107.7. **HRMS-GC-EI** calcd. for $C_{12}H_9N_3O_2S$ $(M)^+$: 259.0415; Found: 259.0403.

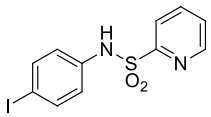


***N*-(4-Methoxyphenyl)pyridine-2-sulfonamide (39).** Compound **39** was prepared



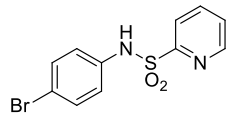
following the typical procedure A from 4-methoxyaniline (493 mg, 4.00 mmol) to give **39** as a white solid; yield: 951 mg (90%); mp = 167-168 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.93 (s, 1H), 8.71 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.98 (td, *J* = 7.7, 1.7 Hz, 1H), 7.86 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.58 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 3.70 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 158.3, 158.1, 150.8, 139.0, 130.8, 127.7, 125.5, 123.5, 114.9, 55.6. **HRMS-ESI** calcd. for $C_{12}H_{13}N_2O_3S$ $(M+H)^+$: 265.0641; Found: 265.0649.

***N*-(4-Iodophenyl)pyridine-2-sulfonamide (40).** Compound **40** was prepared



following the typical procedure A from 4-iodoaniline (876 mg, 4.00 mmol) to give **40** as a white solid; yield: 1.28 g (89%); mp = 193-194 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.34 (bs, 1H, N*H*), 8.69 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.05 (td, *J* = 7.6, 1.7 Hz, 1H), 7.98 (ddd, *J* = 7.9, 1.5, 0.9 Hz, 1H), 7.67 – 7.55 (m, 3H), 7.12 (d, *J* = 8.7 Hz, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 157.8, 151.0, 139.2, 138.8, 128.1, 123.7, 123.6, 123.5, 88.3. **HRMS-ESI** calcd. for $C_{11}H_{10}N_2O_2SI$ $(M+H)^+$: 360.9502; Found: 360.9492.

***N*-(4-Bromophenyl)pyridine-2-sulfonamide (41).** Compound **41** was prepared



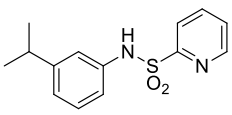
following the typical procedure A from 4-bromoaniline (688 mg, 4.00 mmol) to give **41** as a white solid; yield: 1.09 g (87%); mp = 192-193 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.34 (bs, 1H, N*H*), 8.69 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.04 (td, *J* = 7.6, 1.7 Hz, 1H), 7.98 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.61 (ddd, *J* = 7.4, 4.7, 1.4 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 157.6, 151.0, 139.2, 138.0, 132.8, 128.1, 123.5, 123.4, 117.7. **HRMS-ESI** calcd. for $C_{11}H_{10}N_2O_2SBr$ $(M+H)^+$: 312.9640; Found: 312.9645.

***N*-(4-Chlorophenyl)pyridine-2-sulfonamide (42).** Compound **42** was prepared following the typical procedure A from 4-chloroaniline (510 mg, 4.00 mmol) to give **42** as a white solid; yield: 817 mg (76%); mp = 182-184 ºC. **^{1}H NMR (300 MHz. Acetone-*d*$_6$)** δ (ppm): 9.33 (bs, 1H, N*H*), 8.69 (dd, *J* = 4.5, 1.0 Hz, 1H), 8.10 – 8.00 (m, 1H), 8.00 – 7.94 (m, 1H), 7.61 (ddd, *J* = 7.3, 4.7, 1.4 Hz, 1H), 7.37 – 7.20 (m, 4H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 157.8, 151.0, 139.2, 137.6, 130.1, 129.8, 128.1, 123.5, 123.4. **HRMS-ESI** calcd. for $C_{11}H_{10}N_2O_2SCl$ $(M+H)^+$: 269.0146; Found: 269.0155.

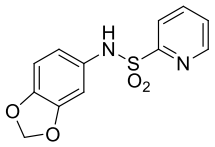
***N*-(4-Fluorophenyl)pyridine-2-sulfonamide (43).** Compound **43** was prepared following the typical procedure A from 4-fluoroaniline (379 µL, 4.00 mmol) to give **43** as a white solid; yield: 797 mg (79%); mp = 156-157 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.21 (bs, 1H, N*H*), 8.70 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.02 (td, *J* = 7.7, 1.7 Hz, 1H), 7.92 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.60 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.36 – 7.22 (m, 2H), 7.01 (t, *J* = 8.8 Hz, 2H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 160.9 (d, $J_{C\text{-}F}$ = 242.0 Hz), 157.9, 150.9, 139.1, 134.7 (d, $J_{C\text{-}F}$ = 2.7 Hz), 127.9, 124.8 (d, $J_{C\text{-}F}$ = 8.3 Hz), 123.5, 116.4 (d, $J_{C\text{-}F}$ = 22.8 Hz). **^{19}F NMR (282 MHz, Acetone-*d*$_6$)** δ (ppm): 57.8 (s). **HRMS-ESI** calcd. for $C_{11}H_{10}N_2O_2FS$ $(M+H)^+$: 253.0441; Found: 253.0437.

Methyl 4-(*N*-(2-pyridyl)sulfonylamino)benzoate (44). Compound **44** was prepared following the typical procedure A from methyl-4-aminobenzoate (605 mg, 4.00 mmol) to give **44** as a white solid; yield: 748 mg (64%); mp = 222-224 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.66 (bs, 1H, N*H*), 8.68 (d, *J* = 4.6 Hz, 1H), 8.07 (d, *J* = 3.5 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.70 – 7.52 (m, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ (ppm): 165.7, 156.3, 150.3, 138.9, 138.2, 130.5, 129.6, 127.6, 124.6, 124.4, 122.5, 120.3, 52.3. **HRMS-ESI** calcd. for $C_{13}H_{13}N_2O_4S$ $(M+H)^+$: 293.0590; Found: 293.0594.

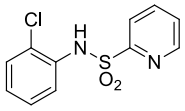
***N*-(3-Isopropylphenyl)pyridine-2-sulfonamide (87).** Compound **87** was prepared following the typical procedure A from 3-isopropylaniline (541 mg, 4.00 mmol) to give **87** as a white solid; yield: 884 mg (80%); mp = 185-186 ºC. **^{1}H NMR (Acetone-d_6, 500 MHz)** δ (ppm): 9.11 (s, 1H), 8.70 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.01 (td, *J* = 7.7, 1.7 Hz, 1H), 7.95 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.59 (ddd, *J* = 7.6, 4.7, 1.3 Hz, 1H), 7.16 – 7.09 (m, 2H), 7.07 (ddd, *J* = 8.0, 2.2, 1.2 Hz, 1H), 6.93 (dt, *J* = 7.6, 1.5 Hz, 1H), 2.78 (h, *J* = 6.9 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (Acetone-d_6, 125 MHz)** δ (ppm): 158.1, 150.9, 150.6, 139.0, 138.5, 129.7, 127.8, 123.6, 123.4, 120.0, 119.5, 34.6, 24.1. **HRMS-GC-EI** calcd. for $C_{14}H_{16}N_2O_2S$ $(M)^+$: 276.0932; Found: 276.0940.



***N*-(Benzo[*d*][1,3]dioxol-5-yl)pyridine-2-sulfonamide (92)**. Compound **92** was prepared following the typical procedure A from 1,3-benzodioxol-5-amine (547 mg, 4.00 mmol) to give **92** as a white solid; yield: 945 mg (85%); mp = 178-179 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ: 9.00 (s, 1H), 8.72 (ddd, *J* = 4.7, 1.7, 0.9, 1H), 8.07 – 7.98 (m, 1H), 7.96 – 7.86 (m, 1H), 7.61 (ddd, *J* = 7.6, 4.7, 1.2, 1H), 6.81 (t, *J* = 1.3, 1H), 6.67 (d, *J* = 1.3, 2H), 5.93 (s, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ: 157.9, 150.9, 148.7, 146.1, 139.1, 132.2, 127.8, 123.5, 116.9, 108.7, 105.4, 102.4. **HRMS-GC-EI** calcd. for $C_{12}H_{10}N_2O_4S$ $(M)^+$: 278.0361; Found: 278.0370.



***N*-(2-Chlorophenyl)pyridine-2-sulfonamide (96).** Compound **96** was prepared following the typical procedure A from 2-chloroaniline (420 µL, 4.00 mmol) to give **96** as a white solid; yield: 892 mg (83 %); mp = 105-106 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.70 (ddd, *J* = 4.6, 1.7, 1.0 Hz, 1H), 8.59 (s, 1H), 8.05 (tt, *J* = 7.8, 1.6 Hz, 1H), 8.00 – 7.90 (m, 1H), 7.69 – 7.59 (m, 2H), 7.38 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.28 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 7.20 – 7.12 (m, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 158.2, 151.1, 139.2, 135.0, 130.5, 128.5, 128.2, 127.9, 127.5, 125.9, 123.2. **HRMS-ESI** calcd. for $C_{11}H_{10}N_2O_2SCl$ $(M+H)^+$: 269.0146; Found: 269.0144.



***N*-(4-Chloro-2-methylphenyl)pyridine-2-sulfonamide (97).** Compound **97** was prepared following the typical procedure A from 4-chloro-2-methylaniline (476 µL, 4.00 mmol) to give **97** as a white solid; yield: 982 mg (94%); mp = 103-104 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.71 (d, *J* = 4.6 Hz, 1H), 7.85 (dd, *J* = 6.7, 1.6 Hz, 2H), 7.49 (ddd, *J* = 6.8, 4.7, 2.1 Hz, 1H), 7.24 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* = 8.6, 2.5 Hz, 1H), 2.23 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 156.7, 150.3, 138.2, 134.6, 132.9, 132.0, 130.9, 127.3, 126.9, 126.1, 123.2, 17.9. **HRMS-GC-EI** calcd. for $C_{11}H_{10}ClN_3O_2S$ $(M)^+$: 283.0182; Found: 283.0181.

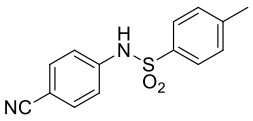
- ***Synthesis of differently substituted N-tosyl and N-nosyl aniline derivatives***

Typical procedure B: To an ice-cooled round-bottomed flask containing a solution of aniline (4.00 mmol, 1.00 equiv) in dry THF (40 mL) were added successively pyridine (388 µL, 4.80 mmol, 1.20 equiv) and the corresponding sulfonyl chloride (4.80 mmol, 1.20 equiv). When the initial self-heating was over, the ice bath was removed and the reacting mixture was warmed up to room temperature and stirred for 16 h. After this time, the resulting mixture was poured into saturated aqueous NH_4Cl (20 mL); the layers were separated and the sulfamide extracted from the aqueous layer (EtOAc, 20 mL). The organic phases were mixed up, washed with brine, dried over $MgSO_4$ and filtered. The resulting residue was purified by SiO_2 flash chromatography employing *n*-Hexane/EtOAc (3:1) as eluent.

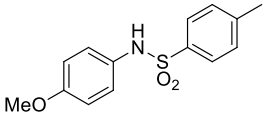
***N*-Phenyl-*p*-toluenesulfonamide (5).** Compound **5** was prepared following the typical procedure B from aniline (364 µL, 4.00 mmol) and *p*-toluenesulfonyl chloride (915 mg, 4.80 mmol) to give **5** as a white solid; yield: 851 mg (86%); mp = 96-97 ºC. **^{1}H NMR (Acetone-d_6, 300 MHz)** δ (ppm): 8.90 (bs, 1H, N*H*), 7.67 (d, *J* = 8.3, 2H), 7.31 (d, *J* = 7.9, 2H), 7.26 – 7.16 (m, 4H), 7.13 – 7.00 (m, 1H), 2.35 (s, 3H). **^{13}C NMR**

(75 MHz, Chloroform-*d*) δ (ppm): 144.0, 136.7, 136.2, 129.8, 129.4, 127.4, 125.4, 121.6, 21.6. **HRMS-GC-EI** calcd. for $C_{13}H_{13}NO_2S$ $(M)^+$: 247.0667; Found: 247.0666.

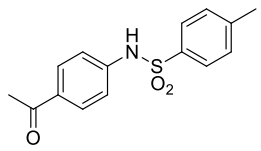
***N*-(4-Cyanophenyl)-*p*-toluenesulfonamide (22).** Compound **22** was prepared following the typical procedure B from 4-aminobenzonitrile (472 mg, 4.00 mmol) and *p*-toluenesulfonyl chloride (915 mg, 4.80 mmol) to give **22** as a white solid; yield: 582 mg (54%); mp = 185-187 ºC. **^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 10.98 (bs, 1H, N*H*), 7.73 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 2.32 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ (ppm): 143.9, 142.3, 136.2, 133.7, 130.0, 126.7, 118.7, 118.4, 105.3, 21.0. **HRMS-GC-EI** calcd. for $C_{14}H_{12}N_2O_2S$ $(M)^+$: 272.0619; Found: 272.0618.



***N*-(4-Methoxyphenyl)-*p*-toluenesulfonamide (45).** Compound **45** was prepared following the typical procedure B from *p*-anisidine (492 mg, 4.00 mmol) and *p*-toluenesulfonyl chloride (915 mg, 4.80 mmol) to give **45** as a light purple solid; yield: 932 mg (84%); mp = 112-114 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.69 – 7.45 (m, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.99 (d, *J* = 8.9 Hz, 2H), 6.83 (s, 1H), 6.74 (d, *J* = 8.9 Hz, 2H), 3.74 (s, 3H), 2.37 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 158.0, 143.8, 136.1, 129.7, 129.1, 127.5, 125.4, 114.5, 55.5, 21.6. **HRMS-GC-EI** calcd. for $C_{14}H_{15}NO_3S$ $(M)^+$: 277.0773; Found: 277.0786.



***N*-(4-Acetylphenyl)-*p*-toluenesulfonamide (46).** Compound **46** was prepared following the typical procedure B from 4'-aminoacetophenone (540 mg, 4.00 mmol) and *p*-toluenesulfonyl chloride (915 mg, 4.80 mmol) to give **46** as a white solid; yield: 868 mg (75%); mp = 196-198 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.85 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.03 (s, 1H), 2.53 (s, 3H), 2.38 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 196.9, 144.6, 141.2,



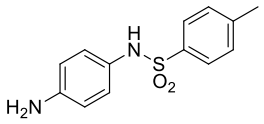
136.0, 133.5, 130.1, 130.0, 127.4, 119.2, 26.5, 21.7. **HRMS-GC-EI** calcd. for $C_{15}H_{15}NO_3S$ $(M)^+$: 289.0773; Found: 289.0761.

***N*-(4-Trifluoromethylphenyl)-*p*-toluenesulfonamide (47).** Compound **47** was prepared following the typical procedure B from 4-(trifluoromethyl)-aniline (502 µL, 4.00 mmol) and *p*-toluenesulfonyl chloride (915 mg, 4.80 mmol) to give **34** as a white solid; yield: 1.13 g (90%); mp = 140-141 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.44 (s, 1H), 7.85 – 7.68 (m, 2H), 7.69 – 7.55 (m, 2H), 7.51 – 7.39 (m, 2H), 7.39 – 7.29 (m, 2H), 2.37 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 145.0, 142.7, 137.8, 130.7, 128.0, 127.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 125.9 (q, $J_{C\text{-}F}$ = 32.2 Hz), 125.3 (q, $J_{C\text{-}F}$ = 268.5 Hz), 120.1, 21.4. **^{19}F NMR (282 MHz, Acetone-d_6)** δ (ppm) 114.9. **HRMS-GC-EI** calcd. for $C_{14}H_{12}F_3NO_2S$ $(M)^+$: 315.0541; Found: 315.0552.

4-(*p*-Tolyl)sulfonamido)benzoic acid (83).[244] To a solution of *p*-amino benzoic acid (3.42 g, 25.0 mmol) and water (15 mL), sodium carbonate (1 N) was added to adjust pH 8. Then *p*-toluenesulfonyl chloride (5.71 g, 30 mmol) was added and the reaction mixture was stirred at rt keeping the pH of the mixture up to 8.0 with occasional addition of sodium carbonate solution. Progress and completion of the reaction was confirmed by TLC. After 2-3 h, the whole mixture was poured into a beaker of pH 2.0. A white solid precipitated, which was filtered and washed several times with water yielding the desired product; yield: 6.55 g (90%); mp = 230-232 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.53 (s, 1H), 7.97 – 7.85 (m, 2H), 7.84 – 7.69 (m, 2H), 7.51 – 7.16 (m, 4H), 2.36 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 167.2, 144.8, 143.3, 137.8, 131.8, 130.6, 128.0, 126.7, 119.4, 21.4. **HRMS-ESI** calcd. for $C_{14}H_{13}NO_4S$ $(M+H)^+$: 292.0632; Found: 292.0648.

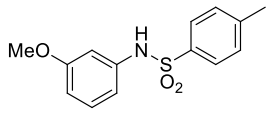
[244] G. Mustafa, I. Ullah Khan, M. Ashraf, I. Afzal, S.A. Shahzad, M. Shafiq , *Bioorg. Med. Chem*. **2012**, *20*, 2535.

***N*-(4-Aminophenyl)-*p*-toluenesulfonamide (84).** To a closed round-bottomed flask



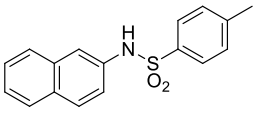
containing the catalyst (10% Pd/C wet, 100 mg, 20% in weight) under inert atmosphere is added a solution of protected nitroaniline ***p*-14** (500 mg, 1.71 mmol) in MeOH (25 mL). Then, a ballon of H_2 is pierced through the septum and with the help of vacuum, reductive atmosphere is made inside. The set reaction is stirred at room temperature overnight. When the reaction is completed, the flask is opened, the suspension filtered through a celite pad to remove the catalyst and the filtrate evaporated to dryness; the resulting crude is further purified by SiO_2 flash chromatography with *n*-Hexane/EtOAc (1:2) as eluent to obtain 400 mg (89 %) of the desired compound as a white solid; mp = 184-186 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.24 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.52 (d, *J* = 8.7 Hz, 2H), 4.54 (s, 2H), 2.36 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 147.4, 143.8, 138.3, 130.1, 128.1, 127.5, 125.9, 115.3, 21.3. **HRMS-ESI** calcd. for $C_{13}H_{15}N_2O_2S$ $(M+H)^+$: 263.0848; Found: 263.0848.

***N*-(3-Methoxyphenyl)-*p*-toluenesulfonamide (86).** Compound **86** was prepared



following the typical procedure B from *m*-anisidine (0.45 mL, 4.00 mmol) and *p*-toluenesulfonyl chloride (915 mg, 4.80 mmol) to give **86** as a light purple solid; yield: 876 mg (79%); mp = 66-68ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.71 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.19 (m, 2H), 7.16 (s, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.71 (t, *J* = 2.3 Hz, 1H), 6.63 (dddd, *J* = 8.2, 4.9, 2.3, 0.9 Hz, 1H), 3.72 (s, 3H), 2.36 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 160.4, 144.0, 138.0, 136.2, 130.1, 129.8, 127.4, 113.4, 111.0, 106.9, 55.4, 21.6. **HRMS-GC-EI** calcd. for $C_{14}H_{15}NO_3S$ $(M)^+$: 277.0773; Found: 277.0766.

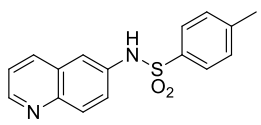
***N*-(2-Naphthyl)-*p*-toluenesulfonamide (93).** Compound **93** was prepared following



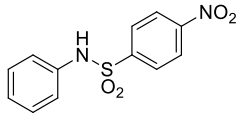
the typical procedure B from 2-naphthylamine (574 mg, 4.00 mmol) and *p*-toluenesulfonyl chloride (915 mg, 4.80 mmol) to give **93** as a white solid; yield: 844 mg (71%); mp = 132-134 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)**

δ (ppm): 7.79 – 7.64 (m, 5H), 7.54 (d, *J* = 2.2 Hz, 1H), 7.43 (pd, *J* = 6.9, 1.5 Hz, 2H), 7.25 – 7.14 (m, 3H), 6.93 (s, 1H), 2.34 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 144.1, 136.2, 134.2, 133.8, 131.3, 129.9, 129.5, 127.8, 127.7, 127.4, 126.9, 125.7, 121.2, 118.6, 21.7. **HRMS-GC-EI** calcd. for $C_{17}H_{15}NO_2S$ $(M)^+$: 297.0824; Found: 297.0822.

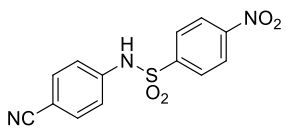
4-Methyl-*N*-(quinolin-6-yl)benzenesulfonamide (108). Compound **108** was prepared following the typical procedure B from quinolin-6-amine (576 mg, 4.00 mmol) and p-toluenesulfonyl chloride (915 mg, 4.80 mmol) to give **108** as a light purple solid; yield: 977 mg (82%). The spectroscopic data (NMR) matched those reported in the literature for 4-methyl-N-(quinolin-6-yl)benzenesulfonamide [CAS: 253328-68-6]. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.85 (s, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.70 – 7.58 (m, 2H), 7.43 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 2.34 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 149.6, 144.3, 136.1, 136.1, 135.1, 130.6, 129.9, 127.3, 124.4, 121.9, 117.4, 21.6.



***N*-Phenyl-4-nitrobenzenesulfonamide (6).** Compound **6** was prepared following the typical procedure B from aniline (364 µL, 4.00 mmol) and 4-nitrobenzenesulfonyl chloride (1.02 g, 4.80 mmol) to give **6** as a pink solid; yield: 989 mg (89%); mp = 125-127ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.42 – 8.27 (m, 2H), 8.14 – 7.91 (m, 2H), 7.33 – 7.18 (m, 4H), 7.18 – 7.03 (m, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 151.0, 146.1, 137.7, 130.1, 129.3, 126.1, 125.0, 122.3. **HRMS-CG-EI$^+$** calcd. for $C_{12}H_{10}N_2O_4S$ $(M)^+$: 278.0361; Found: 278.0365.

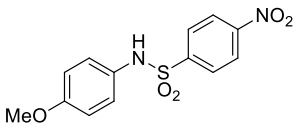


***N*-(4-Cyanophenyl)-4-nitrobenzenesulfonamide (23).** Compound **23** was prepared following the typical procedure B from 4-aminobenzonitrile (472 mg, 4.00 mmol) and 4-nitrobenzenesulfonyl chloride (1.02 g, 4.80 mmol) to give **23** as a light pink solid; yield: 812 mg (67 %); mp = 192-194 ºC. **^{1}H NMR (300 MHz,**



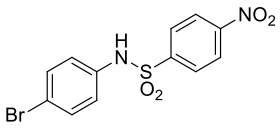
Acetone-d_6) δ (ppm): 8.48 – 8.33 (m, 2H), 8.27 – 8.08 (m, 2H), 7.75 – 7.62 (m, 2H), 7.50 – 7.34 (m, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 151.5, 145.7, 142.2, 134.5, 129.5, 125.5, 120.8, 118.9, 108.6. **HRMS-CG-EI$^+$** calcd. for $C_{13}H_9N_3O_4S$ $(M)^+$: 303.0314; Found: 303.0319.

***N*-(4-Methoxyphenyl)-4-nitrobenzenesulfonamide (48).** Compound **48** was



prepared following the typical procedure B from *p*-anisidine (492 mg, 4.00 mmol) and 4-nitrobenzenesulfonyl chloride (1.02 g, 4.80 mmol) to give **48** as a purple solid; yield: 949 mg (77%); mp = 182-183 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.01 (s, 1H), 8.78 – 8.15 (m, 2H), 8.20 – 7.80 (m, 2H), 7.36 – 6.91 (m, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 3.74 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 158.9, 151.1, 146.3, 130.1, 129.5, 125.8, 125.0, 115.3, 55.7. **HRMS-CG-EI$^+$** calcd. for $C_{13}H_{12}N_2O_5S$ $(M)^+$: 308.0467; Found: 308.0462.

***N*-(4-Bromophenyl)-4-nitrobenzenesulfonamide (49).** Compound **49** was prepared



following the typical procedure B from 4-bromoaniline (688 mg, 4.00 mmol) and 4-nitrobenzenesulfonyl chloride (1.02 g, 4.80 mmol) to give **49** as a beige solid; yield: 1.17 g (82%); mp = 207-208 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.40 (s, 1H), 8.38 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H). **^{13}C NMR (300 MHz, Acetone-d_6)** δ (ppm): 151.3, 145.9, 137.3, 133.2, 129.4, 125.3, 124.1, 118.8. **HRMS-CG-EI$^+$** calcd. for $C_{12}H_9BrN_2O_4S$ $(M)^+$: 355.9466; Found: 355.9465.

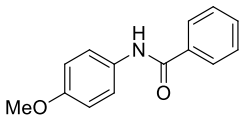
- ***Synthesis of differently substituted anilines protected as amides***[245]

Typical procedure C: To an ice-cooled closed round-bottomed flask containing a solution of aniline (4.00 mmol, 1.00 equiv) and a catalytic amount of DMAP (20 mg) in dry THF (20 mL) were added successively NEt_3 (670 µL, 4.80 mmol, 1.20 equiv) and the corresponding acylating agent (4.80 mmol, 1.2 equiv). When the initial self-heating was over, the ice bath was removed and the reacting mixture was allowed to reach room temperature while stirred for 16 h. After this time, the resulting mixture was poured into saturated aqueous NH_4Cl (20 mL); the layers were separated and the amide extracted from the aqueous layer (EtOAc, 20 mL). The organic phases were mixed up, washed with brine, dried over $MgSO_4$ and filtered. The residue resulting of its evaporation was purified by SiO_2 flash chromatography employing *n*-hexane/EtOAc (4:1) as eluent, except when noted.

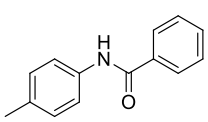
***N*-(4-Cyanolphenyl)benzamide (24).** Compound **24** was prepared following the typical procedure C from 4-aminobenzonitrile (472 mg, 4.00 mmol) and benzoyl chloride (558 µL, 4.80 mmol) to give **24** as a white solid after flash column chromatography (hexane/EtOAc 2:1); 836 mg (94%); mp = 166-168 ºC. **^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 8.04 – 7.94 (m, 4H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.66 – 7.49 (m, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ (ppm): 166.2, 143.5, 134.4, 133.0, 132.0, 128.4, 127.8, 120.2, 119.1, 105.4. **HRMS-GC-EI** calcd. for $C_{14}H_{10}N_2O$ $(M)^+$: 222.0793; Found: 222.0792.

[245] a) T. L. Schneider, K. T. Halloran, J. A. Hillner, R. R. Conry, B. R. Linton, *Chem. Eur. J.* **2013**, *19*, 15101. b) T. Suzuki, M. N. A. Khan, H. Sawada, E. Imai, Y. Itoh, K. Yamatsuta, J. Takeuchi, T. Seko, H. Nakawaga, N. Miyata, *J. Med. Chem.* **2012**, *55*, 5760. c) M. Giese, M. Abrecht, T. Krappitz, M. Peters, V. Gossen, G. Raabe, A. Valkonen, K. Rissanen, *Chem. Commun.* **2012**, *48*, 9983.

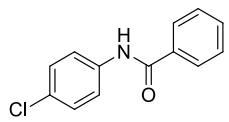
***N*-(4-Methoxyphenyl)benzamide (50).** Compound **50** was prepared following the typical procedure C from *p*-anisidine (492 mg, 4.00 mmol) and benzoyl chloride (558 µL, 4.80 mmol) to give **50** as a white solid; 855 mg (94%); mp = 158-160 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.40 (bs, 1H, N*H*), 8.02 – 7.95 (m, 2H), 7.75 (d, *J* = 9.1 Hz, 2H), 7.59 – 7.44 (m, 3H), 6.92 (d, *J* = 9.1 Hz, 2H), 3.79 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 166.0, 157.1, 136.5, 133.4, 132.1, 129.2, 128.2, 122.7, 114.6, 55.7. **HRMS-GC-EI** calcd. for $C_{14}H_{13}NO_2$ $(M)^+$: 227.0946; Found: 227.0954.



***N*-(4-Methylphenyl)benzamide (51).** Compound **51** was prepared following the typical procedure C from *p*-toluidine (440 µL, 4.00 mmol) and benzoyl chloride (558 µL, 4.80 mmol) to give **51** as a white solid; 803 mg (95%); mp = 150-157 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.88 (bs, 1H, N*H*), 8.47 – 8.41 (m, 2H), 8.18 (d, *J* = 8.5 Hz, 2H), 8.04 – 7.90 (m, 3H), 7.61 (d, *J* = 8.2 Hz, 2H), 2.75 (s, 3H).**^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 166.1, 137.8, 136.4, 133.9, 132.2, 129.9, 129.2, 128.3, 121.1, 20.9. **HRMS-GC-EI** calcd. for $C_{14}H_{13}NO$ $(M)^+$: 211.0997; Found: 211.1007.



***N*-(4-Chlorophenyl)benzamide (52).** Compound **52** was prepared following the typical procedure C from 4-chloroaniline (510 mg, 4.00 mmol) and benzoyl chloride (558 µL, 4.80 mmol) to give **52** as a white solid; 843 mg (91%); mp = 192-195 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.62 (bs, 1H, N*H*), 8.03 – 7.95 (m, 2H), 7.88 (d, *J* = 8.9 Hz, 2H), 7.62 – 7.47 (m, 3H), 7.37 (d, *J* = 8.9 Hz, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 166.4, 139.3, 136.0, 132.5, 129.4, 129.3, 128.9, 128.3, 122.5. **HRMS-GC-EI** calcd. for $C_{13}H_{10}ClN_2O_4S$ $(M)^+$: 231.0451; Found: 231.0453.



***N*-(3-Cyanophenyl)benzamide (88).** Compound **88** was prepared following the typical procedure C from 3-aminobenzonitrile (472 mg, 4.00 mmol) and benzoyl chloride (558 µL, 4.80 mmol) to give **88** as a white solid; 827 mg (93%); mp = 142-144 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.18 (s, 1H), 8.05 (s, 1H), 7.93 – 7.78 (m, 3H), 7.63 – 7.53 (m, 1H), 7.53 – 7.35 (m, 4H). **^{13}C NMR (75 MHz, Acetone-*d6*)** δ (ppm): 166.8, 141.2, 135.5, 132.7, 130.8, 129.3, 128.4, 127.9, 125.2, 123.8, 119.3, 113.3. **HRMS-GC-EI** calcd. for $C_{14}H_{10}N_2O$ $(M)^+$: 222.0793; Found: 222.0790.

***N*-(*o*-Tolyl)benzamide (98).** Compound **98** was prepared following the typical procedure C from *o*-toluidine (429 mg, 4.00 mmol) and benzoyl chloride (558 µL, 4.80 mmol) to give **98** as a white solid; 710 mg (84%); mp = 140-142 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.96 (d, *J* = 8.0 Hz, 1H), 7.92 – 7.81 (m, 2H), 7.68 (s, 1H), 7.61 – 7.43 (m, 3H), 7.26 (td, *J* = 9.7, 6.9 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 2.35 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 165.9, 135.9, 135.0, 131.9, 130.6, 129.8, 128.9, 127.2, 126.9, 125.5, 123.5, 17.9. **HRMS-GC-EI** calcd. for $C_{14}H_{13}NO$ $(M)^+$: 211.0997; Found: 211.0999.

***N*-Phenyl-4-nitrobenzamide (8).** Compound **8** was prepared following the typical procedure C from aniline (364 µL, 4.00 mmol) and 4-nitrobenzoyl chloride (558 µL, 4.80 mmol, 1.2 equiv) to give **8** as a pale yellow solid after flash column chromatography (hexane/EtOAc 1:1); yield: 707 mg (73%); mp = 215-218 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.38 (d, *J* = 9.0 Hz, 2H), 8.35 (d, *J* = 9.0 Hz, 2H), 7.26 (m, 3H), 7.10 (m, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 164.7, 150.6, 142.0, 139.9, 129.8, 129.6, 125.1, 124.4, 121.2. **HRMS-GC-EI** calcd. for $C_{13}H_{10}N_2O_3$ $(M)^+$: 242.0691; Found: 242.0698.

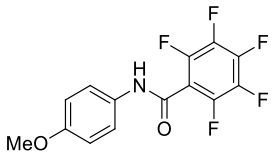
***N*-(4-Cyanophenyl)-4-nitrobenzamide (25).** Compound **25** was prepared following the typical procedure C from 4-aminobenzonitrile (472 mg, 4.00 mmol) and 4-nitrobenzoyl chloride (558 µL, 4.80 mmol) to give **25** as a yellow solid after flash column chromatography (hexane/EtOAc 1:1); yield: 385 mg (36%); mp = 259-261 ºC. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ (ppm): 10.91 (bs, 1H, N*H*), 8.36 (d, *J* = 9.0 Hz, 2H), 8.17 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 9.0 Hz, 2H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ (ppm): 164.6, 149.4, 143.0, 140.0, 133.2, 129.4, 123.6, 120.4, 119.0, 106.0. **HRMS-GC-EI** calcd. for $C_{14}H_9N_3O_3$ $(M)^+$: 267.0644; Found: 267.0637.

2,3,4,5,6-Pentafluoro-*N*-phenylbenzamide (9). Compound **9** was prepared following the typical procedure C from aniline (364 µL, 4.00 mmol) and 2,3,4,5,6-pentafluorobenzoyl chloride (691 µL, 4.80 mmol, 1.20 equiv) to give **9** as a white solid after flash column chromatography (hexane/EtOAc 9:1); yield: 907 mg (79%); mp = 187-189 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 10.00 (s, 1H), 7.74 (dd, *J* = 8.8, 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.19 (tt, *J* = 7.5, 2.3 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-d$_6$)** δ (ppm): 156.0, 144.8 (dm, $J_{C\text{-}F}$ = 249.7 Hz), 142.9 (dm, $J_{C\text{-}F}$ = 259.0 Hz), 139.0, 138.5 (dm, $J_{C\text{-}F}$ = 257.1 Hz), 129.0, 125.8, 120.7, 114.1-113.4 (m). **^{19}F NMR (282 MHz, Acetone-*d*$_6$)** δ (ppm): 34.57 – 34.23 (m), 23.18 – 22.79 (m), 14.54 – 14.13 (m). **HRMS-GC-EI** calcd. for $C_{13}H_6F_5NO$ (M^+): 287.0370, found: 287.0359.

2,3,4,5,6-Pentafluoro-*N*-(4-cyanophenyl)benzamide (26). Compound **26** was prepared following the typical procedure C from 4-aminobenzonitrile (472 mg, 4.00 mmol) and 2,3,4,5,6-pentafluorobenzoyl chloride (691 µL, 4.80 mmol) to give **26** as a white solid; yield: 649 mg (52%); mp = 142-144 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 10.40 (bs, 1H, N*H*), 7.94 (d, *J* = 8.6 Hz, 2H), 7.81 (d, *J* = 8.6 Hz, 2H). **^{13}C NMR (125 MHz, Chloroform-*d*)** δ (ppm): 155.8, 144,4 (dm, $J_{C\text{-}F}$ = 256.2 Hz), 143.0 (dm, $J_{C\text{-}F}$ = 257.5

Hz), 141.0, 137.9 (dm, $J_{C\text{-}F}$ = 256.2 Hz), 133.6, 120.3, 118.6, 111.2-110.9 (m), 108.5. **^{19}F NMR (282 MHz, Acetone-d_6)** δ (ppm): 34.9 – 34.8 (m), 24.08 (t, *J* = 20.2 Hz), 14.8 – 14.6 (m). **HRMS-GC-EI** calcd. for $C_{14}H_5F_5N_2O$ (M^+): 312.0322; Found: 312.0317.

2,3,4,5,6-Pentafluoro-*N*-(4-methoxyphenyl)benzamide (53). Compound **53** was prepared following the typical procedure C from *p*-anisidine (492 mg, 4.00 mmol) and 2,3,4,5,6-pentafluorobenzoyl chloride (691 µL, 4.80 mmol) to give **53** as a white solid; yield: 1.01 g (79%); mp = 201-203 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.84 (bs, 1H, N*H*), 7.65 (d, *J* = 9.1 Hz, 2H), 6.96 (d, *J* = 9.1 Hz, 2H), 3.81 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** (with the C-F signals omitted) δ (ppm): 157.9, 155.6, 132.1, 122.3, 122.2, 115.0, 55.8. **^{19}F NMR (282 MHz, Acetone-d_6)** δ (ppm): 34.4 – 34.3 (m), 22.7 – 22.6 (m), 14.3 – 14.2 (m). **HRMS-GC-EI** calcd. for $C_{14}H_8F_5NO_2$ (M^+): 317.0475; Found: 317.0466.

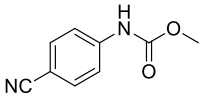


- ***Synthesis of differently substituted anilines protected as carbamates***[246]

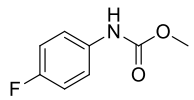
Typical procedure D: To an ice-cooled closed round-bottomed flask containing a solution of aniline (1.00 equiv) in dry THF (20 mL) were added successively pyridine (1.20 equiv) and the corresponding carbamoyl chloride (1.20 equiv). When initial self-heating finished, the ice bath was removed and the reacting mixture was allowed to reach room temperature while stirred for 24 h. After this time, the resulting mixture was evaporated and triturated with Et_2O, the solid was then colected and washed well with cold Et_2O. If needed, the resulting solid was purified by SiO_2 flash chromatography employing *n*-hexane/EtOAc (4:1) as eluent.

[246] a) P. R. Sultane, T. B. Mete, R. G. Bhat, *Org. Biomol. Chem.* **2014**, *12*, 261. b) M. C. Davis, *Synthetic Communications*, **2007***, 37*, 2079.

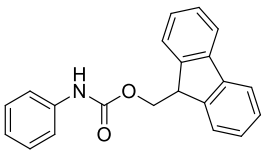
Methyl (4-cyanophenyl)carbamate (27). Compound **27** was prepared according to the typical procedure D from 4-aminobenzonitrile (472 mg, 4.00 mmol) to give **27** as a white solid; yield: 550 mg (78%); mp = 150-152 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.13 (s, 1H), 7.96 – 7.09 (m, 4H), 3.74 (s, 3H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 154.6, 144.4, 133.9, 119.5, 119.0, 106.1, 52.6. **HRMS-GC-EI** calcd. for $C_9H_8N_2O_2$ (M^+): 176.0586, found: 176.0585.



Methyl (4-fluorophenyl)carbamate (54). Compound **54** was prepared according to the typical procedure D from 4-fluoroaniline (379 µL, 4.00 mmol) to give **54** as a white solid; yield: 568 mg (84%); mp = 92-94ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 8.62 (s, 1H), 7.77 – 7.37 (m, 2H), 7.37 – 6.52 (m, 2H), 3.69 (s, 3H). **^{13}C NMR (Acetone-*d*$_6$, 75 MHz)** δ (ppm): 159.3 (d, $J_{C\text{-}F}$ = 237.7 Hz), 155.1, 136.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 120.9 (d, $J_{C\text{-}F}$ = 7.5 Hz), 116.0 (d, $J_{C\text{-}F}$ = 22.5 Hz), 52.2. **^{19}F NMR (282 MHz, Acetone-*d*$_6$)** δ (ppm): 55.2 (s). **HRMS-GC-EI** calcd. for $C_8H_8NO_2$ (M^+): 169.0539; Found: 169.0546.



(9*H*-Fluoren-9-yl)methyl-(4-methoxyphenyl)carbamate (11). Compound **11** was prepared according to the typical procedure D from aniline (91 µL, 1.00 mmol) to give **11** as a white solid; yield: 230 mg (73%); mp = 188-189 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 8.85 (bs, 1H, N*H*), 7.87 (d, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 7.7 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 2H), 7.37 – 7.25 (m, 4H), 7.02 (d, *J* = 7.4, 1.1 Hz, 1H), 4.50 (d, *J* = 6.8 Hz, 2H), 4.30 (t, *J* = 6.8 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 154.4, 145.0, 142.2, 140.2, 129.6, 128.6, 128.0, 126.0, 123.5, 120.9, 119.3, 67.0, 48.0.



9*H*-Fluoren-9-yl)methyl-(4-cyanophenyl)carbamate (28). Compound **28** was prepared according to the typical procedure D from 4-aminobenzonitrile (118 mg, 1.00 mmol) to give **28** as a white solid; yield: 205 mg (60%); mp = 194-197 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.30 (s, 1H), 7.87 (dt, *J* = 7.6, 1.0 Hz, 2H), 7.77 – 7.58 (m, 6H), 7.46 – 7.38 (m, 2H), 7.33 (td, *J* = 7.4, 1.3 Hz, 2H), 4.57 (d, *J* = 6.6 Hz, 2H), 4.31 (t, *J* = 6.6 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 154.1, 144.8, 144.4, 142.2, 134.0, 128.6, 128.0, 125.9, 120.9, 119.5, 119.2, 106.3, 67.4, 47.8. **HRMS-ESI** calcd. for $C_{22}H_{17}N_2O_2$ $(M+H)^+$: 341.1284; Found: 341.1297.

(9*H*-Fluoren-9-yl)methyl-(4-methoxyphenyl)carbamate (55). Compound **55** was prepared according to the typical procedure D from *p*-anisidine (123 mg, 1.0 mmol) to give **55** as a white solid; yield: 252 mg (73%); mp = 179-181 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm) 8.66 (s, 1H), 7.88 (dt, *J* = 7.6, 1.0 Hz, 2H), 7.73 (d, *J* = 7.5 Hz, 2H), 7.49 – 7.38 (m, 4H), 7.33 (td, *J* = 7.4, 1.3 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 4.47 (d, *J* = 6.9 Hz, 2H), 4.29 (t, *J* = 6.0 Hz, 1H), 3.76 (s, 3H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 159.3, 156.5, 154.6, 145.1, 142.2, 133.2, 128.6, 127.9, 126.0, 120.8, 114.8, 66.9, 55.7, 48.0. **HRMS-ESI** calcd. for $C_{22}H_{20}NO_3$ $(M+H)^+$: 346.1437; Found: 346.1454.

- ***Synthesis of differently substituted anilines protected as ureas***

***Typical procedure E*:**[247] To an ice-cooled closed round-bottomed flask containing a solution of phenyl isocyanate (4.00 mmol, 1.00 equiv) in dry DCM (15 mL) was added, dropwise, dimethylamine (8 M in water, 16.00 mmol, 4.00 equiv). When the initial self-heating was over, the ice bath was removed and the reacting mixture was allowed to reach rt while stirred for 16 h. After this time, the resulting mixture was extracted with saturated aqueous $NaHCO_3$ (3 x 10 mL). The organic

[247] B. A. Hopkins, J. P. Wolfe, *Angew. Chem. Int. Ed.* **2012**, *51*, 9886.

phase was dried over $MgSO_4$ and filtered. After solvent evaporation the desired protected anilines as ureas are obtained with high yields as solid materials.

***Typical procedure F*:**[248] To an ice-cooled closed round-bottomed flask containing a solution of the corresponding aniline (4.00 mmol, 1.00 equiv) and 10% of DMAP, in dry pyridine (8 mL), was added, dropwise, dimethylcarbamic chloride (previously distilled, 4.80 mmol, 1.20 equiv). When the initial self-heating was over, the ice bath was removed and the reacting mixture is allowed to reach room temperature while stirred for 16 h. After this time, the resulting mixture was extracted with HCl (1 M) (3 x 10 mL). The organic phase was dried over $MgSO_4$ and filtered. The residual crude mixture was purified by SiO_2 flash chromatography employing *n*-hexane/EtOAc (1:2) as eluent, yielding the corresponding ureas as stable solids.

1,1-Dimethyl-3-phenylurea (12). Compound **12** was prepared following the typical procedure E from isocyanatobenzene (0.43 mL, 4.00 mmol) and dimethylamine (8 M) (2.0 mL) to give **12** as a white solid, 571 mg (87%); mp = 113-115 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 7.70 (s, 1H), 7.60 – 7.45 (m, 2H), 7.31 – 7.10 (m, 2H), 7.04 – 6.83 (m, 1H), 2.98 (s, 6H). **HRMS-GC-EI** calcd. for $C_9H_{12}N_2O$ (M^+): 164.0950, found: 164.0952.

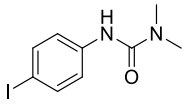
3-(4-Cyanophenyl)-1,1-dimethylurea (29). Compound **29** was prepared following the typical procedure E from 4-isocyanatobenzonitrile (576 mg, 4.00 mmol) and dimethylamine (8 M) (2.0 mL) to give **29** as a white solid, 926 mg (70%); mp = 156-157 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 8.15 (s, 1H), 7.92 – 7.65 (m, 2H), 7.65 – 7.31 (m, 2H), 3.01 (s, 6H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 155.8, 146.1, 133.4, 119.9, 119.8, 104.8, 36.5. **HRMS-ESI** calcd. for $C_{10}H_{12}N_3O$ $(M+H)^+$: 190.0974; Found: 190.0971.

3-(4-Methoxyphenyl)-1,1-dimethylurea (56). Compound **56** was prepared following

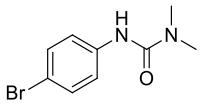
[248] B. Kuhn, P. Mohr, M. Stahl, *J. Medical Chemistry*, **2010**, *53*, 2601.

the typical procedure E from 1-isocyanato-4-methoxybenzene (0.52 mL, 4.00 mmol) and dimethylamine (8 M) (2.0 mL) to give **56** as a white solid, 660 mg (85%); mp = 113-115 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.48 – 7.02 (m, 2H), 6.99 – 6.55 (m, 2H), 6.26 (s, 1H), 3.69 (s, 3H), 2.90 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 156.4, 155.5, 132.4, 122.5, 113.8, 55.4, 36.3. **HRMS-GC-EI** calcd. for $C_{10}H_{14}N_2O_2$ (M^+): 194.1055; Found: 194.1047.

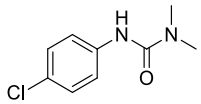
3-(4-Iodophenyl)-1,1-dimethylurea (57). Compound **57** was prepared following the typical procedure F from 4-iodoaniline (870 mg, 4.00 mmol) and dimethylcarbamic chloride (0.46 mL, 4.80 mmol) to give **57** as a light orange solid, 986 mg (85%); mp = 185-187 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.80 – 7.40 (m, 2H), 7.39 – 6.96 (m, 2H), 6.36 (s, 1H), 3.00 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 155.5, 139.2, 137.8, 121.8, 85.7, 36.6. **HRMS-ESI** calcd. for $C_9H_{12}N_2OI$ $(M+H)^+$: 290.9988; Found: 291.0001.



3-(4-Bromophenyl)-1,1-dimethylurea (58). Compound **58** was prepared following the typical procedure F from 4-bromoaniline (686 mg, 4.00 mmol) and dimethylcarbamic chloride (0.46 mL, 4.80 mmol) to give **58** as a light orange solid, 680 mg (70%); mp = 170-172 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.32 – 7.25 (m, 2H), 7.23 – 7.15 (m, 2H), 6.26 (s, 1H), 2.93 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 155.6, 138.5, 131.7, 121.6, 115.4, 36.5. **HRMS-ESI** calcd. for $C_9H_{12}N_2OBr$ $(M+H)^+$: 243.0127; Found: 243.0134.



3-(4-Chlorophenyl)-1,1-dimethylurea (59). Compound **59** was prepared following the typical procedure F from 4-chloroaniline (510 mg, 4.00 mmol) and dimethylcarbamic chloride (0.46 mL, 4.80 mmol) to give **59** as a white solid, 514 mg (65%); mp = 150-153 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.32 (d, *J* = 8.8 Hz, 2H), 7.22



(d, *J* = 8.8 Hz, 2H), 6.38 (s, 1H), 3.01 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm) 155.6, 138.0, 128.8, 127.9, 121.2, 36.6. **HRMS-GC-EI** calcd. for $C_9H_{11}N_2OCl$ (M^+): 198.0560; Found: 198.0561.

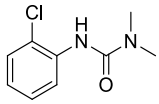
3-(4-Fluorophenyl)-1,1-dimethylurea (60). Compound **60** was prepared following the typical procedure F from 4-fluoroaniline (510.38 mL, 4.00 mmol) and dimethylcarbamic chloride (0.46 mL, 4.80 mmol) to give **60** as a white solid, 451 mg (62%); mp = 142-144 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.35 – 7.28 (m, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 6.26 (s, 1H), 3.02 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 158.9 (d, $J_{C\text{-}F}$ = 240.0 Hz), 156.1, 134.3 (d, $J_{C\text{-}F}$ = 2.2 Hz), 122.2 (d, $J_{C\text{-}F}$ = 7.5 Hz), 115.3 (d, $J_{C\text{-}F}$ = 21.7 Hz), 36.5. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -120.4. **HRMS-ESI** calcd. for $C_9H_{12}N_2OF$ $(M+H)^+$: 183.0928; Found: 183.0922.

3-(2-Methoxyphenyl)-1,1-dimethylurea (99). Compound **99** was prepared following the typical procedure E from 1-methoxy-2-isocyanatobenzene (0.53 mL, 4.00 mmol) and dimethylamine (8 M) (2.0 mL) to give **99** as a yellow oil, 621 mg (80%); **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.23 – 7.91 (m, 1H), 7.06 (s, 1H), 6.98 – 6.87 (m, 2H), 6.90 – 6.75 (m, 1H), 3.85 (s, 3H), 3.01 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 155.2, 147.4, 128.9, 121.5, 120.7, 118.5, 109.5, 55.5, 36.0. **HRMS-GC-EI** calcd. for $C_{10}H_{14}N_2O_2$ $(M)^+$: 194.1055; Found: 194.1052.

3-(2-Fluorophenyl)-1,1-dimethylurea (100). Compound **100** was prepared following the typical procedure E from 1-fluoro-2-isocyanatobenzene (0.46 mL, 4.00 mmol) and dimethylamine (8 M) (2.0 mL) to give **100** as a white solid, 532 mg (73%); mp = 84-86 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.12 (td, *J* = 8.2, 1.7 Hz, 1H), 7.16 – 6.80 (m, 3H), 6.57 (s, 1H), 3.03 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 155.1, 152.6 (d, $J_{C\text{-}F}$ = 239.0 Hz), 127.7 (d, $J_{C\text{-}F}$ = 9.7 Hz), 124.4 (d, $J_{C\text{-}F}$ = 3.0 Hz), 122.7 (d, $J_{C\text{-}F}$ = 7.5 Hz), 121.5 (d, $J_{C\text{-}F}$ = 1.5 Hz), 114.4 (d, $J_{C\text{-}F}$ = 19.5 Hz), 36.3. **^{19}F NMR**

(282 MHz, Chloroform-*d*) δ (ppm): -132.7. **HRMS-GC-EI** calcd. for $C_9H_{11}N_2OF$ $(M)^+$: 182.0855; Found: 182.0847.

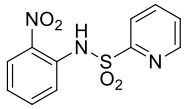
3-(2-Chlorophenyl)-1,1-dimethylurea (101). Compound **101** was prepared following the typical procedure E from 1-chloro-2-isocyanatobenzene (0.48 mL, 4.00 mmol) and dimethylamine (8 M) (2.0 mL) to give **101** as a white solid, 580 mg (73%); mp = 93-95 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.24 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.26 – 7.18 (m, 1H), 6.99 (s, 1H), 6.93 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 3.06 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 154.7, 135.9, 128.4, 127.4, 122.7, 122.1, 120.6, 36.1. **HRMS-GC-EI** calcd. for $C_9H_{11}N_2OCl$ $(M)^+$: 198.0560; Found: 198.0553.



4.2.2. Copper-catalyzed mononitration of protected anilines

***Typical procedure G*:** A 20 mL vessel was charged with the corresponding *N*-protected aniline (0.20 mmol) and copper(II)nitrate (3.76 mg, 0.02 mmol, 10 mol%). The reaction vessel was sealed with a Teflon lined aluminium cap, then evacuated and flushed with oxygen three times. Under the atmosphere of oxygen, acetonitrile (1.0 mL) and HNO_3 (13μL, 0.20 mmol) were added via syringe. The reaction was then heated at the corresponding temperature for the indicated time. When the reaction was finished, the mixture was diluted with EtOAc (5.0 mL) and washed twice with $NaHCO_3$ (sat.) reextracting next the aqueous phase with EtOAc (3 x 5.0 mL). The combined organic layers were then dried over $MgSO_4$ and filtered. The crude obtained after solvent evaporation was purified by SiO_2 flash cromatography using the optimal *n*-Hexane/EtOAc mixture as eluent to provide the corresponding pure nitrocompound.

***N*-(2-Nitrophenyl)pyridine-2-sulfonamide (*o*-2).** Compound ***o*-2**, obtained together with ***p*-2**, was prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **1** (83.71 mg, 0.40 mmol) and HNO_3 (26 μL, 0.40 mmol) to give ***o*-2** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield: 50.34

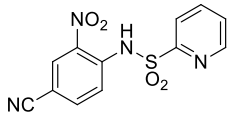


mg (45%); mp = 98-101 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 9.94 (bs, 1H, N*H*), 8.59 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.10 (dd, *J* = 8.4, 1.5 Hz, 1H), 8.06 – 7.97 (m, 2H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.58 (ddd, *J* = 8.4, 7.4, 1.6 Hz, 1H), 7.48 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.18 (ddd, *J* = 8.4, 7.4, 1.3 Hz, 1H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 156.5, 150.3, 138.5, 135.6, 133.7, 129.3, 127.5, 126.0, 124.3, 122.6, 122.2. **HRMS-GC-EI** calcd. for $C_{11}H_{19}N_3O_4S$ (M^+): 279.0314; Found: 279.0322.

***N*-(2-Nitrophenyl)pyridine-2-sulfonamide (*p*-2).** Compound ***p*-2**, obtained together with ***o*-2**, was prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **1** (83.71 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***p*-2** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:1); yield: 59.22 mg (53%). mp = 253-254 ºC. **^{1}H NMR(Acetone-d_6, 300 MHz)** δ (ppm): 8.69 (dt, *J* = 4.7 Hz, 1.3, 1H), 8.16 (d, *J* = 9.3 Hz, 2H), 8.13 (d, *J* = 1.4 Hz, 1H), 8.12 (t, *J* = 1.4 Hz, 1H), 7.72 – 7.62 (m, 1H), 7.55 (d, *J* = 9.3 Hz, 2H). **^{13}C NMR (Acetone-d_6, 125 MHz)** δ (ppm): 157.5, 151.2, 145.1, 144.4, 139.6, 128.6, 125.8, 123.5, 119.6. **HRMS-GC-EI** calcd. for $C_{11}H_9N_3O_4S$ $(M)^+$: 279.0314; Found: 279.0301.

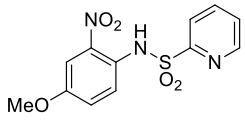
***N*-(4-Methyl-2-nitrophenyl)pyridine-2-sulfonamide (4).** Compound **4** was prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **3** (49.73 mg, 0.2 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **4** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield: 55.71 mg (95%); mp = 100-103 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 9.72 (bs, 1H, N*H*), 8.55 (d, *J* = 4.6 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.88 (td, *J* = 7.6, 1.6 Hz, 1H), 7.85 – 7.76 (m, 2H), 7.46 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.36 (dd, *J* =8.5, 1.8 Hz, 1H), 2.32 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 157.4, 151.1, 140.8, 139.7, 136.8, 136.6, 131.1, 128.6, 126.4, 124.3, 123.4, 20.3. **HRMS-GC-EI** calcd. for $C_{12}H_{11}N_3O_4S$ (M^+): 293.0470; Found: 293.0472.

***N*-(4-Cyano-2-nitrophenyl)pyridine-2-sulfonamide (30).** Compound **30** was



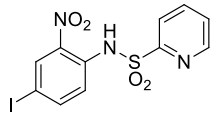
prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **21** (51.82 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **30** as a pale yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:1); yield: 60.24 mg (99%); mp = 125-129 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.64 (d, *J* = 4.4 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.13 – 7.98 (m, 2H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.67 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.56 (ddd, *J* = 7.2, 4.7, 1.3 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 160.1, 150.5, 144.8, 141.3, 139.4, 136.7, 130.1, 127.5, 123.3, 122.8, 118.4, 102.1. **HRMS-GC-EI** calcd. for $C_{12}H_8ClN_4O_4S$ (M^+): 304.0266, found: 304.0268.

***N*-(4-Methoxy-2-nitrophenyl)pyridine-2-sulfonamide (61).** Compound **61** was



prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **39** (52.93 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **61** as a dark yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield: 60.67 mg (98%); mp = 76-79 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 9.40 (bs, 1H, N*H*), 8.54 (d, *J* = 4.5 Hz, 1H), 7.95 – 7.82 (m, 3H), 7.50 –7.41 (m, 2H), 7.14 (dd, *J* = 9.2, 3.0 Hz, 1H), 3.80 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 156.4, 156.3, 150.0, 140.0, 138.3, 127.2, 125.9, 125.1, 122.3, 122.2, 109.1, 55.9. **HRMS-GC-EI** calcd. for $C_{12}H_{11}N_3O_5S$ (M^+): 309.0419; Found: 309.0408.

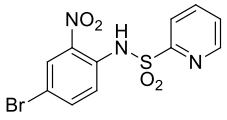
***N*-(4-Iodo-2-nitrophenyl)pyridine-2-sulfonamide (62).** Compound **62** was prepared



following the typical procedure G (2 h, 50 ºC) from sulfonylated aniline **40** (72.03 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **62** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 5:1); yield: 44.65 mg (55%); mp = 135-137 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.78 (s, 1H), 8.63 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 8.39 (d, *J* = 2.1 Hz, 1H), 8.19 – 7.94 (m, 3H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.68 (ddd, *J* = 7.2, 4.7, 1.6 Hz, 1H). **^{13}C NMR (75 MHz,**

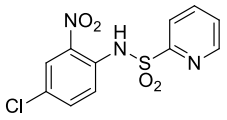
Acetone-d_6) δ (ppm): 157.3, 151.1, 144.6, 140.9, 139.9, 134.8, 133.8, 128.8, 125.7, 123.4, 87.2. **HRMS-ESI** calcd. for $C_{11}H_9N_3O_4IS$ $(M+H)^+$: 405.9353; Found: 405.9351.

***N*-(4-Bromo-2-nitrophenyl)pyridine-2-sulfonamide (63).** Compound **63** was



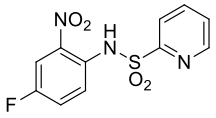
prepared following the typical procedure G (1 h, 80 ºC) from sulfonylated aniline **41** (62.69 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **63** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield: 55.27 mg (77%); mp = 99-102 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.77 (s, 1H), 8.63 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 8.25 (dd, *J* = 2.1, 0.6 Hz, 1H), 8.19 – 8.00 (m, 2H), 7.99 – 7.83 (m, 2H), 7.69 (ddd, *J* = 7.3, 4.7, 1.5 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 157.3, 151.1, 141.1, 139.9, 138.8, 133.3, 129.1, 128.8, 126.0, 123.4, 117.3. **HRMS-GC-EI** calcd. for $C_{11}H_8N_3O_4BrS$ $(M)^+$: 356.9419; Found: 356.9410.

***N*-(4-Chloro-2-nitrophenyl)pyridine-2-sulfonamide (64).** Compound **64** was



prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **42** (53.85 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **64** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield: 55.87 mg (89%); mp = 87-88 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 9.79 (bs, 1H, N*H*), 8.51 (d, *J* = 4.6 Hz, 1H), 8.04 – 7.99 (d, *J* = 2.5 Hz, 1H), 7.99 – 7.91 (m, 2H), 7.86 (d, *J* = 7.8, 1.7 Hz, 1H), 7.52 – 7.39 (m, 2H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 156.5, 150.3, 138.6, 138.5, 135.6, 132.4, 129.9, 127.7, 125.6, 123.8, 122.5. **HRMS-GC-EI** calcd. for $C_{11}H_8ClN_3O_4S$ (M^+): 312.9924; Found: 312.9932.

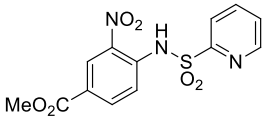
***N*-(4-Fluoro-2-nitrophenyl)pyridine-2-sulfonamide (65).** Compound **65** was



prepared following the typical procedure G (1 h, 100ºC) from sulfonylated aniline **43** (50.48 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **65** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield:

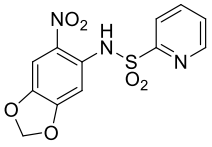
49.30 mg (83%); mp = 113-114 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 9.62 (s, 1H), 8.62 – 8.49 (m, 1H), 8.07 – 7.96 (m, 2H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.77 (dd, *J* = 8.2, 3.0 Hz, 1H), 7.49 (ddd, *J* = 7.6, 4.7, 1.3 Hz, 1H), 7.33 (ddd, *J* = 9.7, 7.1, 3.0 Hz, 1H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 158.1 (d, J_{C-F} = 248.0 Hz), 156.5, 150.2, 139.1 (d, J_{C-F} = 7.5Hz), 138.6, 129.9 (d, J_{C-F} = 3.0 Hz), 127.6, 125.1 (d, J_{C-F} = 8.2 Hz), 123.0 (d, J_{C-F} = 22.5 Hz), 122.4, 112.6 (d, J_{C-F} = 27.0 Hz). **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -114.5. **HRMS-GC-EI** calcd. for $C_{11}H_8N_3O_4FS$ $(M)^+$: 297.0220; Found: 297.0222.

Methyl 3-nitro-4-(pyridine-2-sulfonamido)benzoate (66). Compound **66** was



prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **44** (58.55 mg, 0.2 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **66** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:1); yield: 53.94 mg (80%); mp = 78-81 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 10.21 (bs, 1H, N*H*), 8.77 (d, *J* = 2.0 Hz, 1H), 8.59 (d, *J* = 4.7 Hz, 1H), 8.18 (d, *J* = 8.8, 2.0 Hz, 1H), 8.14 – 8.03 (m, 2H), 7.95 (td, *J* = 7.8, 1.7 Hz, 1H), 7.52 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 3.91 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 164.5, 156.2, 150.4, 138.6, 137.6, 136.8, 136.1, 127.9, 127.7, 125.8, 122.6, 121.0, 52.8. **HRMS-GC-EI** calcd. for $C_{13}H_{11}N_3O_6S$ (M^+): 337.0369; Found: 337.0381.

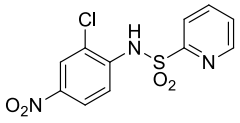
***N*-(6-Nitrobenzo[*d*][1,3]dioxol-5-yl)pyridine-2-sulfonamide (94).** Compound **94**



was prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **92** (55.67 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **94** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 4:1); yield: 52.45 mg (81%); mp = 164-166 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.23 (s, 1H), 8.64 (ddd, *J* = 4.8, 1.6, 1.0 Hz, 1H), 8.20 – 8.03 (m, 2H), 7.69 (ddd, *J* = 6.7, 4.7, 1.9 Hz, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 6.22 (s, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 157.2, 154.7, 151.2, 145.7, 139.9, 133.7, 132.3,

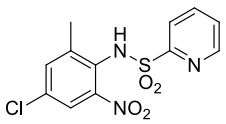
128.8, 123.5, 105.4, 104.9, 102.5. **HRMS-ESI** calcd. for $C_{12}H_{10}N_3O_6S$ $(M+H)^+$: 324.0284; Found: 324.0286.

***N*-(2-Chloro-4-nitrophenyl)pyridine-2-sulfonamide (102).** Compound **102** was



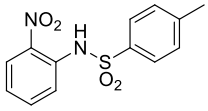
prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **96** (53.77 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **102** as a pale yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:1); yield: 47.02 mg (75%); mp = 87-88 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.26 (bs, 1H, N*H*), 8.71 (d, *J* = 4.7 Hz, 1H), 8.28 (d, *J* = 2.6 Hz, 1H), 8.20 (dd, *J* = 9.0, 2.6 Hz, 1H), 8.16 – 8.08 (m, 2H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.75 – 7.67 (ddd, *J* = 6.4, 4.7, 1.6 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 157.7, 151.2, 145.0, 141.6, 139.7, 128.8, 125.9, 125.8, 124.0, 123.3, 123.0. **HRMS-GC-EI** calcd. for $C_{11}H_8ClN_3O_4S$ 312.9924 (M^+); Found: 312.9932.

***N*-(4-Chloro-2-nitrophenyl)pyridine-2-sulfonamide (103).** Compound **103** was



prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **97** (56.62 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **103** as a beige solid after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield: 55.74 mg (85%); mp = 176-177 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.70 – 8.50 (m, 1H), 8.06 (td, *J* = 7.8, 1.7 Hz, 1H), 7.86 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.79 (d, *J* = 2.5 Hz, 1H), 7.74 – 7.60 (m, 2H), 2.34 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 158.8, 151.1, 149.9, 144.0, 139.5, 135.7, 133.5, 128.3, 128.1, 123.5, 122.6, 18.9. **HRMS-ESI** calcd. for $C_{12}H_{11}{}^{35}ClN_3O_6S$ $(M+H)^+$: 328.0153; Found: 328.0156.

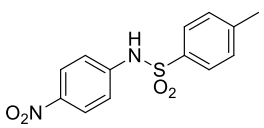
***N*-(2-Nitrophenyl)-*p*-toluenesulfonamide (*o*-14).** Compound ***o*-14**, obtained



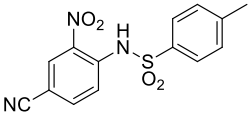
together with ***p*-14**, was prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **5** (98.9 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***o*-14** as a yellow solid after purification through flash column chromatography (hexane/AcOEt 4:1); yield: 52.6 mg (45%); mp = 102-104 ºC. **^{1}H NMR (300 MHz,**

Chloroform-*d*) δ (ppm): 9.84 (bs, 1H, N*H*), 8.14 – 8.07 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.84 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.58 (ddd, *J* = 8.6, 7.4, 1.6 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.16 (ddd, *J* = 8.6, 7.4, 1.3 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.0, 137.2, 136.0, 135.9, 134.1, 130.1, 127.4, 126.3, 123.9, 121.2, 21.7. **HRMS-GC-EI** calcd. for $C_{13}H_{12}N_2O_4S$ (M^+): 292.0518, found: 292.0529.

***N*-(4-Nitrophenyl)-*p*-toluenesulfonamide (*p*-14).** Compound ***p*-14**, obtained together with ***o*-14**, was prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **5** (98.9 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***p*-14** as a yellow solid after purification through flash column chromatography (hexane/AcOEt 2:1) yield: 52.7 mg (45%); mp = 193-194 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.78 (bs, 1H, N*H*), 8.15 (d, *J* = 9.2 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 9.1 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 2.37 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 145.3, 145.2, 137.6, 130.8, 128.1, 126.0, 119.3, 21.4. **HRMS-GC-EI** calcd. for $C_{13}H_{12}N_2O_4S$ (M^+): 292.0518, found: 292.0511.



***N*-(4-Cyano-2-nitrophenyl)-*p*-toluenesulfonamide (31).** Compound **31** was prepared following the typical procedure G (1 h, 100 ºC) from tosylated aniline **22** (54.50 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **31** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:2).; yield: 59.73 mg (94%); mp = 140-141 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.16 (bs, 1H, N*H*), 8.57 (d, *J* = 1.8 Hz, 1H), 8.04 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.98 – 7.91 (m, 3H), 7.43 (d, *J* = 8.6 Hz, 2H), 2.41 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 146.3, 139.2, 138.1, 137.8, 136.6, 131.6, 131.0, 128.5, 121.4, 117.3, 107.4, 21.5. **HRMS-GC-EI** calcd. for $C_{14}H_{11}N_3O_4S$ (M^+): 317.0470; Found: 317.0475.



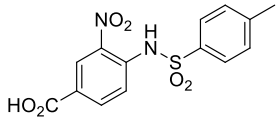
***N*-(4-Methoxy-2-nitrophenyl)-*p*-toluenesulfonamide (67).** Compound **67** was prepared following the typical procedure G (1 h, 100 ºC) from tosylated aniline **45** (55.59 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **67** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 4:1); yield: 58.04 mg (90 %); mp = 98-100 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 9.23 (s, 1H), 7.77 (d, *J* = 9.1 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 3.0 Hz, 1H), 7.24 – 7.09 (m, 3H), 3.80 (s, 3H), 2.36 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 156.3, 144.7, 139.1, 135.6, 130.0, 127.2, 126.6, 124.8, 123.1, 109.2, 56.1, 21.7. **HRMS-GC-EI** calcd. for $C_{14}H_{14}N_2O_5S$ $(M)^+$: 322.0623; Found: 322.0633. Compound **67** was also prepared following Method G on a 1.00-mmol scale, using tosylated aniline **45** (278 mg, 1.00 mmol), HNO_3 (65 µL, 1.00 mmol) and $Cu(NO_3)_2$ (18.51 mg, 0.10 mmol) in 5 mL of MeCN. The title compound **67** was isolated in 76 % yield (245 mg).

***N*-(4-Acetyl-2-nitrophenyl)-*p*-toluenesulfonamide (68).** Compound **68** was prepared following the typical procedure G (1 h, 100 ºC) from tosylated aniline **46** (57.97 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **68** as a light yellow solid after purification through flash column chromatograph (*n*-Hexane/EtOAc 3:1); yield: 51.55 mg (77%); mp = 113-114 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.08 (s, 1H), 8.66 (d, *J* = 2.1 Hz, 1H), 8.25 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.03 – 7.74 (m, 3H), 7.43 (d, *J* = 8.2 Hz, 2H), 2.61 (s, 3H), 2.40 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 195.3, 146.1, 137.9, 137.8, 136.8, 135.6, 133.0, 131.0, 128.5, 127.1, 120.8, 26.5, 21.5. **HRMS-ESI** calcd. for $C_{15}H_{15}N_2O_5S$ $(M+H)^+$: 335.0696; Found: 335.0709.

***N*-(4-Trifluoromethylphenyl)-*p*-toluenesulfonamide (69).** Compound **69** was prepared following the typical procedure G (1 h, 100 ºC) from tosylated aniline **47** (63.18 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **69** as a yellow oil after purification through flash column chromatography

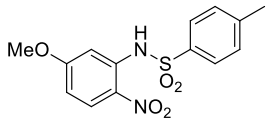
(*n*-Hexane/EtOAc 6:1); yield: 54.88 mg (76 %). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 10.13 (s, 1H), 8.40 (dd, *J* = 2.1, 1.0 Hz, 1H), 7.96 (dd, *J* = 8.9, 1.0 Hz, 1H), 7.86 – 7.67 (m, 3H), 7.34 – 7.29 (m, 2H), 2.39 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.5, 137.1, 135.5, 135.4, 132.3 (q, $J_{C\text{-}F}$ = 3.0 Hz), 130.3, 127.4, 125.3 (q, $J_{C\text{-}F}$ = 34.5 Hz), 122.7 (q, $J_{C\text{-}F}$ = 270.0 Hz), 124.0 (q, $J_{C\text{-}F}$ = 3.7 Hz), 120.6 ; 21.6. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm) -62.7. **HRMS-GC-EI** calcd. for $C_{14}H_{11}F_3N_2O_4S$ $(M)^+$: 360.0392; Found: 360.0390.

4-(4-Methylphenylsulfonamido)-3-nitrobenzoic acid (85). Compound **85** was



prepared following the typical procedure G (2 h, 50ºC) from tosylated aniline **83** (58.38 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol). The reaction mixture was diluted with 10 mL of AcOEt and the organic phase was extracted with a solution of NaOH (1 M) (4 x 5 mL).[249] The aqueous phases were combined and acidified until pH 5, then it was extracted with EtOAc (4 x 10 mL), dried over Na_2SO_4, providing, without further purification after evaporation, the desired product as a light yellow solid in 75% yield (50.57 mg) ; mp = 199-202 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.70 (d, *J* = 2.0 Hz, 1H), 8.26 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.06 – 7.74 (m, 3H), 7.53 – 7.26 (m, 2H), 2.40 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ (ppm): 165.1, 144.3, 140.7, 136.1, 134.9, 134.7, 130.0, 127.1, 127.0, 126.6, 123.0, 21.0. **HRMS-ESI** calcd. for $C_{14}H_{12}N_2NaO_6S$ $(M+Na)^+$: 359.0308; Found: 359.0323.

***N*-(5-Methoxy-2-nitrophenyl)-*p*-toluenesulfonamide (*o*-89).** Compound ***o*-89** (obtained together with ***p*-89**) was prepared following the typical procedure G (1 h, 100 ºC) from tosylated aniline **86** (55.5 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give ***o*-89** as a light yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 3:1); yield: 21.3 mg (33%); mp = 131-133 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.18 (s, 1H), 8.15 (d, *J* = 9.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.60 – 7.34 (m, 2H), 7.21 (d, *J* = 2.7 Hz,



[249] When this organic phase was evaporated, the nitrodecarboxilative product was achieved. No starting material was observed.

1H), 6.80 (dd, *J* = 9.4, 2.7 Hz, 1H), 3.92 (s, 3H), 2.39 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 166.2, 145.9, 137.1, 136.9, 131.5, 131.0, 129.5, 128.4, 111.0, 104.9, 56.8, 21.5. **HRMS-ESI** calcd. for $C_{14}H_{15}N_2O_5S$ $(M+H)^+$: 323.0696; Found: 323.0707.

***N*-(3-Methoxy-4-nitrophenyl)-*p*-toluenesulfonamide (*p*-89).** Compound ***p*-89** (obtained together with ***o*-89**) was prepared following the typical procedure G (1 h, 100 ºC) from tosylated aniline **86** (55.5 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give ***p*-89** as a light yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 3:1); yield: 25.1 mg (39%); mp = 167-169 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.68 (s, 1H), 8.21 – 7.66 (m, 3H), 7.39 (ddd, *J* = 7.9, 1.3, 0.7 Hz, 2H), 7.14 (d, *J* = 2.2 Hz, 1H), 6.92 (dd, *J* = 8.9, 2.2 Hz, 1H), 3.91 (s, 3H), 2.38 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 155.2, 145.3, 144.9, 137.5, 135.9, 130.8, 128.1, 128.0, 110.6, 104.0, 56.9, 21.4. **HRMS-ESI** calcd. for $C_{14}H_{15}N_2O_5S$ $(M+H)^+$: 323.0696; Found: 323.0691.

***N*-(2-Naphthyl)-*p*-toluenesulfonamide (95).** Compound **95** was prepared following the typical procedure G (1 h, 100 ºC) from tosylated aniline **93** (59.55 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **95** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield: 39.76 mg (58%); mp = 159-161 ºC. **^{1}H NMR (300 MHz, Benzene-d_6)** δ (ppm): 8.51 (s, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.63 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.57 – 7.45 (m, 2H), 7.22 (dd, *J* = 9.1, 0.8 Hz, 1H), 7.15 – 7.10 (m, 1H), 7.02 – 6.78 (m, 2H), 6.69 – 6.35 (m, 2H), 1.67 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 145.3, 141.5, 137.8, 133.3, 132.3, 130.7, 130.4, 129.2, 128.7, 128.1, 128.1, 125.8, 123.3, 122.3, 21.4. **HRMS-ESI** calcd. for $C_{17}H_{14}N_2NaO_4S$ $(M+Na)^+$: 365.0566; Found: 365.0553. A not separable mixture of dinitrocompounds was also isaloted in 17% yield; **HRMS-ESI** calcd. for $C_{17}H_{13}N_3NaO_6S$ $(M+Na)^+$: 410.0417; Found: 410.0428.

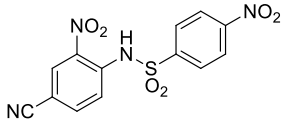
4-Methyl-*N*-(5-nitroquinolin-6-yl)benzenesulfonamide (109). Compound **109** was prepared following the typical procedure G (1 h, 50 ºC) from 4-methyl-*N*-(quinolin-6-yl)benzenesulfonamide **108** (59.6 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **109** as an orange oil after purification through flash column chromatography (*n*-Hexane/EtOAc 10:1); yield: 56.93 mg (84%). The spectroscopic data (NMR) matched those reported in the literature for 4-methyl-N-(5-nitroquinolin-6-yl)benzenesulfonamide [CAS: 500349-85-9]. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.91 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 8.31 – 8.23 (m, 1H), 8.20 – 8.14 (m, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.54 (dd, *J* = 8.8, 4.2 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 2H), 2.36 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 150.8, 145.1, 144.8, 136.2, 135.7, 135.5, 131.1, 130.3, 129.8, 127.2, 124.1, 123.4, 121.8, 21.7.

4-Nitro-*N*-(2-nitrophenyl)benzenesulfonamide (*o*-15). Compound ***o*-15**, obtained together with ***p*-15**, was prepared following the typical procedure G (1 h, 100 ºC) from sulfonylated aniline **6** (55.7 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give ***o*-15** as a yellow solid after purification through flash column chromatography (hexane/AcOEt 1:1); yield: 19.3 mg (30%); mp = 170-171 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.86 (s, 1H), 8.47 – 8.34 (m, 2H), 8.24 – 8.15 (m, 2H), 8.10 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.86 – 7.67 (m, 2H), 7.50 – 7.31 (m, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 151.7, 145.6, 141.0, 136.4, 132.5, 129.8, 126.9, 126.7, 125.5, 124.4. **HRMS-ESI** calcd. for $C_{12}H_9N_3NaO_6S$ $(M+Na)^+$: 346.0104; Found: 346.0117.

4-Nitro-*N*-(4-nitrophenyl)benzenesulfonamide (*p*-15). Compound ***p*-15**, obtained together with ***o*-15**, was prepared following the typical procedure G (1 h, 100 ºC) from protected aniline **6** (55.7 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give ***p*-15** as a light yellow solid after purification through flash column chromatography (hexane/AcOEt 1:1); yield: 35.6 mg (55%);

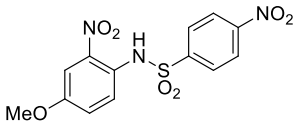
mp = 144-147 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.47 – 8.36 (m, 2H), 8.28 – 8.10 (m, 4H), 7.58 – 7.40 (m, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 151.6, 145.7, 145.0, 144.2, 129.6, 126.1, 125.5, 120.2. **HRMS-ESI** calcd. for $C_{12}H_8N_3O_6S$ $(M-H)^-$: 322.0139; Found: 322.0151.

4-Nitro-*N*-(4-cyano-2-nitrophenyl)benzenesulfonamide (32). Compound **32** was



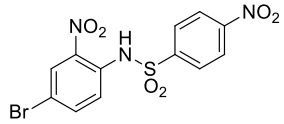
prepared following the typical procedure G (1 h, 100 ºC) from protected aniline **23** (60.68 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **32** as a yellow solid after purification through column chromatography (*n*-Hexane/EtOAc 2:1); yield: 67.64 mg (97%); mp = 269-271 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.39 – 8.25 (m, 2H), 8.22 – 8.10 (m, 2H), 8.02 (d, *J* = 2.1 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.57 (dd, *J* = 8.9, 2.1 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 150.9, 150.2, 146.2, 142.5, 136.1, 129.6, 129.0, 124.7, 122.6, 118.8, 100.3. **HRMS-ESI** calcd. for $C_{13}H_7N_4O_6S$ $(M-H)^-$: 347.0091; Found: 347.0096.

4-Nitro-*N*-(4-methoxy-2-nitrophenyl)benzenesulfonamide (70). Compound **70** was



prepared following the typical procedure G (1 h, 100 ºC) from protected aniline **48** (61.74 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **70** as a light yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:1); yield: 63.62 mg (90%); mp = 162-164 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.38 (s, 1H), 8.39 (d, *J* = 9.0 Hz, 2H), 8.02 (d, *J* = 9.1 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 3.0 Hz, 1H), 7.33 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.90 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 158.9, 151.5, 145.8, 144.3, 129.6, 129.2, 125.4, 123.9, 122.0, 110.7, 56.6. **HRMS-ESI** calcd. for $C_{13}H_{11}N_3NaO_7S$ $(M+Na)^+$: 376.0209; Found: 376.0209.

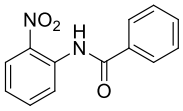
4-Nitro-*N*-(4-bromo-2-nitrophenyl)benzenesulfonamide (71). Compound **71** was



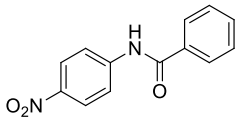
prepared following the typical procedure G (2 h, 50 ºC) from protected aniline **49** (71.47 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **71** as a light yellow solid

after purification through flash column chromatography (*n*-Hexane/EtOAc 1:1); yield: 61.17 mg (76%); mp = 164-168 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.83 (bs, 1H, N*H*), 8.42 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 2.3 Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 2H), 7.91 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 151.7, 145.4, 141.7, 138.9, 131.8, 129.8, 129.4, 126.4, 125.6, 118.3. **HRMS-GC-EI** calcd. for $C_{12}H_8BrN_3O_6S$ (M^+): 400.9317; Found: 400.9313.

***N*-(2-Nitrophenyl)benzamide (*o*-16).** Compound ***o*-16**, obtained together with ***p*-16**, was prepared following the typical procedure G (14 h, 100 ºC) from benzalinilide **7** (78.9 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***o*-16** as a yellow solid after purification through flash column chromatography (hexane/AcOEt 4:1); yield: 31.00 mg (32%); mp = 94-95 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 11.33 (bs, 1H, N*H*), 9.00 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.27 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.99 (d, *J* = 6.8 Hz, 2H), 7.71 (ddd, *J* = 8.6, 7.6, 1.6 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.22 (ddd, *J* = 8.6, 7.6, 1.4 Hz, 1H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 165.9, 136.6, 136.3, 135.5, 134.2, 132.8, 129.2, 127.5, 126.0, 123.4, 122.3. **HRMS-GC-EI** calcd. for $C_{13}H_{10}N_2O_3$ (M^+) 242.0691, found: 242.0693.



***N*-(4-Nitrophenyl)benzamide (*p*-16).** Compound ***p*-16**, obtained together with ***o*-16**, was prepared following the typical procedure G (14 h, 100 ºC) from benzanilide **7** (78.9 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***p*-16** as a yellow solid after purification through flash column chromatography (*n*-hexane/AcOEt 4:1); yield: 34.9 mg (36%); mp = 200-202 ºC. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ (ppm): 10.81 (s, 1H), 8.27 (d, *J* = 9.2 Hz, 2H), 8.07 (d, *J* = 9.2 Hz, 2H), 8.03 – 7.83 (m, 2H), 7.75 – 7.44 (m, 3H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ (ppm): 166.2, 146.6, 142.4, 134.3, 132.0, 128.4, 127.9, 124.8, 119.7. **HRMS-GC-EI** calcd. for $C_{13}H_{10}N_2O_3$ (M^+) 242.0691, found: 242.0695.



***N*-(4-Cyano-2-nitrophenyl)benzamide (33).** Compound **33** was prepared following the typical procedure G (12 h, 100 ºC) from benzanilide **24** (44.54 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **33** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield: 46.05 mg (86%); mp = 145-147 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 11.22 (s, 1H, N*H*), 8.99 (d, *J* = 8.8 Hz, 1H), 8.70 (d, *J* = 2.0 Hz, 1H), 8.17 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.04 (d, *J* = 7.0 Hz, 2H), 7.75 – 7.59 (m, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 166.3, 139.2, 139.1, 138.2 134.6, 133.9, 131.2, 130.0, 128.3, 123.8, 117.6, 107.6. **HRMS-ESI** calcd. for $C_{14}H_9N_3O_3Na$, $(M+Na)^+$: 290.0536; Found: 290.0540.

***N*-(4-Methoxy-2-nitrophenyl)benzamide (72).** Compound **72** was prepared following the typical procedure G (16 h, 100 ºC) from benzanilide **50** (45.52 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **72** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 4:1); yield: 46.34 mg (85%); mp = 139-141 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.63 (bs, 1H, N*H*), 8.54 (d, *J* = 9.2 Hz, 1H), 8.08 – 7.91 (m, 2H), 7.69 (d, *J* = 3.0 Hz, 1H), 7.67 – 7.53 (m, 3H), 7.40 (dd, *J* = 9.2, 3.0 Hz, 1H), 3.93 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 165.9, 156.6, 140.4, 135.4, 133.1, 129.8, 128.5, 128.1, 125.7, 123.0, 109.9, 56.4. **HRMS-ESI** calcd. for $C_{14}H_{13}N_2O_4$ $(M+H)^+$: 273.0870; Found: 273.0688.

***N*-(4-Methyl-2-nitrophenyl)benzamide (73).** Compound **73** was prepared following the typical procedure G (16 h, 100 ºC) from benzanilide **51** (42.37 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **73** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 4:1); yield: 36.96 mg (72%); mp = 145-146 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 11.22 (bs, 1H, N*H*), 8.87 (d, *J* = 8.6 Hz, 1H), 8.06 (d, *J* = 1.3 Hz, 1H), 8.04 – 7.93 (m, 2H), 7.65 – 7.43 (m, 4H), 2.41 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 165.8, 137.2,

136.5, 134.3, 133.7, 133.1, 132.6, 129.1, 127.5, 125.8, 122.2, 20.7. **HRMS-GC-EI** calcd. for $C_{14}H_{12}N_2O_3$ (M^+) 256.0848; Found: 256.0847.

***N*-(4-Chloro-2-nitrophenyl)benzamide (74).** Compound **74** was prepared following the typical procedure G (16 h, 100 ºC) from benzanilide **52** (46.36 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **74** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 4:1); yield: 45.94 mg (83%); mp = 133-135 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 11.23 (s, 1H), 8.99 (d, *J* = 9.2 Hz, 1H), 8.24 (d, *J* = 2.5 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.68 – 7.48 (m, 4H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 165.7, 136.6, 136.2, 134.2, 133.8, 133.0, 129.2, 128.6, 127.5, 125.6, 123.5. **HRMS-GC-EI** calcd. for $C_{13}H_9{}^{35}ClN_2O_3$ (M^+): 276.0302; Found: 276.0305. Compound **74** was also prepared following the typical procedure G on multigram scale, using benzoylated aniline **52** (1.80 g, 7.76 mmol), HNO_3 (0.52 mL, 11.70 mmol, 1.50 equiv) and $Cu(NO_3)_2$ (145 mg, 0.77 mmol) in 20 mL of MeCN over 72 h. The title compound **74** was isolated in 72 % yield (1.55 g).

***N*-(3-Cyano-nitrophenyl)benzamide (91).** Compound **91** was prepared following the typical procedure G (4 h, 100 ºC) from benzanilide **88** (44.84 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **91** as a complex mixture of three regioisomers. These regiosimers were detected by GC-Mass spectrometry. However, it was not possible to isolate each compound due to the complexity of the mixture. Peak 1 (starting material **88**); **HRMS-ESI** calcd. for $C_{14}H_{10}N_2O$, $(M)^+$: 222.0793, found: 222.0791. Peak 2 (mononitro product 1); **HRMS-ESI** calcd. for $C_{14}H_9N_3O_2$, $(M)^+$: 267.0644, found: 267.0641. Peak 3 (mononitro product 2); **HRMS-ESI** calcd. for $C_{14}H_9N_3O_2$, $(M)^+$: 267.0644, found: 267.0634. Peak 4 (mononitro product 3); **HRMS-ESI** calcd. for $C_{14}H_9N_3O_2$, $(M)^+$: 267.0644, found: 267.0634.

***N*-(2-Methyl-nitrophenyl)benzamide (104).** Compound **104** was prepared following the typical procedure G (2 h, 100 ºC) from benzanilide **98** (42.25 mg, 0.2 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **104** as an inseparable 3:1 mixture of ***p*-104** and ***o*-104** regioisomers. These regiosimers were detected by GC-Mass spectrometry. Peak 1 (starting material **98**); **HRMS-ESI** calcd. for $C_{14}H_{13}NO$, $(M)^+$: 211.0997 found: 211.0975. Peak 2 (mononitro product 1, mayor, ***p*-104**); **HRMS-ESI** calcd. for $C_{14}H_{12}N_3O_3$, $(M)^+$: 256.0848, found: 256.0855. Peak 3 (mononitro product 2 minor, ***o*-104**); **HRMS-ESI** calcd. for $C_{14}H_{12}N_3O_3$, $(M)^+$: 256.0848, found: 256.0850.

4-Nitro-*N*-(2-nitrophenyl)benzamide (*o*-17). Compound ***o*-17**, obtained together with ***p*-17**, was prepared following the typical procedure G (16 h, 100 ºC) from benzanilide **8** (96.9 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***o*-17** as a yellow solid after purification through flash column chromatography (*n*-hexane/AcOEt 1:1); yield: 28.7 mg (25%); mp = 271-273 ºC. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ (ppm): 11.06 (bs, 1H, N*H*), 8.41 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 8.8 Hz, 2H), 8.04 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.83 – 7.71 (m, 2H), 7.48 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ (ppm): 163.9, 149.6, 143.4, 139.1, 134.1, 130.8, 129.3, 126.5, 126.3, 125.1, 123.9. **HRMS-ESI** calcd. for $C_{13}H_9N_3O_5$ (M^+) 287.0542, found: 287.0553.

4-Nitro-*N*-(4-nitrophenyl)benzamide (*p*-17). Compound ***p*-17**, obtained together with ***o*-17**, was prepared following the typical procedure G (16 h, 100 ºC) from benzanilide **8** (96.9 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***p*-17** as a pale yellow solid after purification through flash column chromatography (*n*-hexane/AcOEt 1:1); yield: 34.5 mg (30%); mp = 271-275 ºC. **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ (ppm): 11.07 (bs, 1H, N*H*), 8.39 (d, *J* = 8.8 Hz, 2H), 8.29 (d, *J* = 9.2 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 9.3 Hz, 2H). **^{13}C NMR (75 MHz, DMSO-*d*$_6$)** δ (ppm): 164.7, 149.4, 144.9, 142.9, 139.8, 129.5, 124.8, 123.6, 120.1. **HRMS-ESI** calcd. for $C_{13}H_9N_3O_5$ (M^+): 287.0542, found: 287.0536.

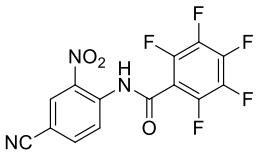
4-Nitro-*N*-(4-cyano-2-nitrophenyl)benzamide (34). Compound **34** was prepared following the typical procedure G (16 h, 100 ºC) from benzanilide **25** (53.44 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **34** as a pale yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:1); yield: 14.41 mg (23%); mp = 210-213 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 11.24 (s, 1H), 8.88 (d, *J* = 8.8 Hz, 1H), 8.72 (d, *J* = 2.0 Hz, 1H), 8.61 – 8.43 (m, 2H), 8.35 – 8.27 (m, 2H), 8.22 (dd, *J* = 8.8, 2.0 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 164.9, 151.4, 140.1(1), 140.1(3), 139.1, 138.2, 131.1, 129.9, 125.1, 124.5, 117.5, 108.5. **HRMS-CG-EI** calcd. for $C_{14}H_8N_4O_5$ (M^+): 312.0495; Found: 312.0510.

2,3,4,5,6-Pentafluoro-*N*-(2-nitrophenyl)benzamide (*o*-18). Compound ***o*-18**, obtained together with ***p*-18**, was prepared following the typical procedure G (16 h, 100 ºC) from pentafluorobenzanilide **9** (114.9 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***o*-18** as a white solid after purification through flash column chromatography (*n*-hexane/AcOEt 9:1); yield: 27.9 mg (21%); mp = 149-152 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 10.92 (bs, 1H, N*H*), 8.87 (dd, *J* = 8.5, 1.2 Hz, 1H), 8.29 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.75 (ddd, *J* = 8.5, 7.4, 1.5 Hz, 1H), 7.32 (ddd, *J* = 8.5, 7.4, 1.3 Hz, 1H).**^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 156.9, 145.3 (dm, $J_{C\text{-}F}$ = 249.0 Hz), 143.6 (dm, $J_{C\text{-}F}$ = 249.0 Hz), 141.0, 138.7 (dm, $J_{C\text{-}F}$ = 234.0 Hz), 136.0, 132.6, 126.7, 126.5, 125.1, 113.1-112.5 (m). **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): 35.37 – 35.19 (m), 26.73 – 26.53 (m), 16.13 – 15.88 (m). **HRMS-GC-EI** calcd. for $C_{13}H_5F_5N_2O_3$ (M^+): 332.0220, found: 332.0232.

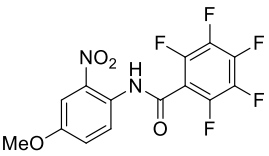
2,3,4,5,6-Pentafluoro-*N*-(4-nitrophenyl)benzamide (*p*-18). Compound ***p*-18**, obtained together with ***o*-18**, was prepared following the typical procedure G (16 h, 100 ºC) from pentafluorobenzanilide **9** (114.9 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***p*-18** as a white solid after

purification through flash column chromatography (hexane/AcOEt 9:1); yield: 43.9 mg (33%); mp = 152-154 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.62 (s, 1H), 8.62 – 8.20 (m, 2H), 8.12 – 7.69 (m, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 156.7, 145.0, 144.9 (dm, $^{1}J_{C\text{-}F}$ = 250.1 Hz), 144.6, 143.4 (dm, $^{1}J_{C\text{-}F}$ = 253.9 Hz), 138.6 (dm, $^{1}J_{C\text{-}F}$ = 249.0 Hz), 125.8, 120.6, 113.0 (m). **^{19}F NMR (282 MHz, Acetone-d_6)** δ (ppm): 34.9 – 34.8 (m), 24.2 – 24.0 (m), 14.9 – 14.8 (m). **HRMS-GC-EI^{+}**, calcd. for $C_{13}H_5F_5N_2O_3$ (M^{+}): 332.0220, found: 332.0227.

2,3,4,5,6-Pentafluoro-*N*-(4-cyano-2-nitrophenyl) benzamide (35). Compound **35** was prepared following the typical procedure G (16 h, 100 ºC) from pentafluorobenzanilide **26** (62.41 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **35** as a beige solid after purification through flash column chromatography (*n*-Hexane/EtOAc 4:1); yield: 8.62 mg (12%); mp = 191-194 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.71 (d, *J* = 8.8 Hz, 1H), 8.68 (d, *J* = 1.9 Hz, 1H), 8.23 (dd, *J* = 8.7, 2.0 Hz, 1H). **^{19}F NMR (282 MHz, Acetone-d_6)** δ (ppm): 39.9 – 39.7 (m), 30.0 – 29.8 (m), 19.4 –19.2 (m). **HRMS-GC-EI** calcd. for $C_{14}H_4F_5N_3O_3$ (M^{+}): 357.0173; Found: 357.0184.



2,3,4,5,6-Pentafluoro-*N*-(4-methoxy-2-nitrophenyl)benzamide (75). Compound **75** was prepared following the typical procedure (16 h, 100 ºC) from pentafluorobenzanilide **53** (63.42 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **75** as a white solid after purification through flash column chromatography (*n*-Hexane/EtOAc 4:1); yield: 40.51 mg (56%); mp = 132-133 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.32 (bs, 1H, N*H)*, 8.16 (d, *J* = 9.1 Hz, 1H), 7.66 (d, *J* = 3.0 Hz, 1H), 7.40 (dd, *J* = 9.1, 3.0 Hz, 1H), 3.95 (s, 3H). **^{13}C NMR (125 MHz, Acetone-d_6)** δ (ppm): 158.1, 156.7, 145.2 (dm, $J_{C\text{-}F}$ = 245.1 Hz), 143.4 (dm, $J_{C\text{-}F}$ = 253.7 Hz), 142.3, 138.6 (dm, $J_{C\text{-}F}$ = 250.0 Hz), 127.4, 125.1, 121.9, 113.1-112.7 (m), 110.4, 57.1. **^{19}F NMR (282 MHz, Acetone-d_6)** δ (ppm): 35.0 – 34.9 (m), 24.0 – 23.8 (m), 14.5 – 14.3 (m). **HRMS-GC-EI** calcd. for $C_{14}H_7F_5N_2O_4$ (M^{+}): 362.0326; Found: 362.0341.



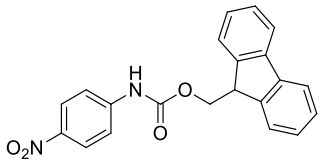
Methyl (4-cyano-2-nitrophenyl)carbamate (36). Compound **36** was prepared following the typical procedure G (12 h, 100 ºC) from protected aniline **27** (52.85 mg, 0.30 mmol) and HNO_3 (19 µL, 0.30 mmol) to give **36** as a pale yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 10:1); yield: 59.12 mg (89%); mp = 145-147 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.90 (s, 1H), 8.66 (d, *J* = 8.9 Hz, 1H), 8.64 (d, *J* = 1.9 Hz, 1H), 8.10 (dd, *J* = 8.9, 2.0 Hz, 1H), 3.84 (s, 3H). **^{13}C NMR** (**75 MHz, Acetone-d_6**) δ (ppm): 153.9, 139.5, 139.1, 137.4, 131.3, 122.3, 117.6, 106.7, 53.6. **HRMS-GC-EI** calcd. for $C_9H_7N_3O_4$ (M^+): 221.0437; Found: 221.0429.

Methyl (4-fluoro-2-nitrophenyl)carbamate (76). Compound **76** was prepared following the typical procedure G (16 h, 100 ºC) from protected aniline **54** (33.83 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **76** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 10:1); yield: 38.56 mg (90%); mp = 114-115 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.47 (s, 1H), 8.40 (dd, *J* = 9.4, 5.1 Hz, 1H), 7.95 (dd, *J* = 8.8, 3.1 Hz, 1H), 7.60 (dddd, *J* = 9.4, 7.5, 3.1, 0.5 Hz, 1H), 3.78 (s, 3H). **^{13}C NMR** (**75 MHz, Acetone-d_6**) δ (ppm): 157.7 (d, $J_{C\text{-}F}$ = 243.0 Hz), 154.4, 138.6 (d, $J_{C\text{-}F}$ = 4.5 Hz), 132.3 (d, $J_{C\text{-}F}$ = 2.2 Hz), 124.4 (d, $J_{C\text{-}F}$ = 8.2 Hz), 123.7 (d, $J_{C\text{-}F}$ = 22.5 Hz), 113.0 (d, $J_{C\text{-}F}$ = 27.7 Hz), 53.2. **^{19}F NMR (282 MHz, Acetone-d_6)** δ (ppm): 58.0. **HRMS-GC-EI** calcd. for $C_8H_7N_2O_4$ (M^+): 214.0390; Found: 214.0386.

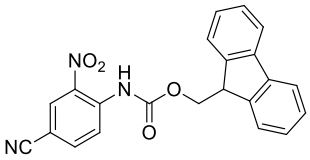
(9*H*-Fluoren-9-yl)methyl(2-nitrophenyl)carbamate (*o*-19). Compound ***o*-19**, obtained together with ***p*-19**, was prepared following the typical procedure G (16 h, 100 ºC) from Fmoc protected aniline **11** (126.1 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***o*-19** as a yellow solid after purification through flash column chromatography (*n*-hexane/AcOEt 4:1); yield: 41.8 mg (29%); mp = 146-148 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.71 (bs, 1H, N*H*), 8.33 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.88

(d, *J* = 7.5 Hz, 2H), 7.78 – 7.69 (m, 3H), 7.43 (t, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.4, 1.1 Hz, 2H), 7.28 (d, *J* = 8.4, 7.4, 1.1 Hz, 1H), 4.56 (d, *J* = 6.9 Hz, 2H), 4.36 (t, *J* = 6.9 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 153.8, 144.7, 142.2, 136.3, 135.4, 128.7, 128.1, 126.6, 126.0, 124.0, 122.4, 120.9, 68.2, 47.8. **HRMS-ESI** calcd. for $C_{21}H_{17}N_2O_4$ $(M+H)^+$: 361.1183; found: 361.1182.

(9*H*-Fluoren-9-yl)methyl(4-nitrophenyl)carbamate (*p*-19). Compound ***p*-19**, obtained together with ***o*-19**, was prepared following the typical procedure G (16 h, 100 ºC) from Fmoc protected aniline **11** (126.1 mg, 0.40 mmol) and HNO_3 (26 µL, 0.40 mmol) to give ***p*-19** as a pale yellow solid after purification through flash column chromatography (*n*-hexane/AcOEt 4:1); yield: 56.2 mg (39%); mp = 165-168 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.50 – 9.42 (bs, 1H, N*H*), 8.18 (d, *J* = 9.3 Hz, 2H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.76 (d, *J* = 9.2 Hz, 2H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.33 (td, *J* = 7.4, 1.2 Hz, 2H), 4.58 (d, *J* = 6.6 Hz, 2H), 4.31 (t, *J* = 6.6 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 154.0, 146.3, 144.8, 143.4, 142.2, 128.6, 128.0, 125.9, 125.7, 120.9, 118.7, 67.5, 47.8. **HRMS-ESI** calcd. for $C_{21}H_{16}N_2O_4Na$ $(M+Na)^+$: 383.1002; found: 383.0998.

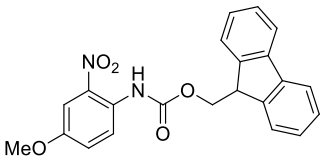


(9*H*-Fluoren-9-yl)methyl(4-cyano-2-nitrophenyl)carbamate (37). Compound **37** was prepared following the typical procedure G (12 h, 100 ºC) from Fmoc protected aniline **28** (102.10 mg, 0.30 mmol) and HNO_3 (19.5 µL, 0.30 mmol) to give **37** as a pale yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 10:1); yield: 65.98 mg (57%); mp = 201-204 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 10.18 (s, 1H), 8.73 (d, *J* = 9.0 Hz, 1H), 8.55 (d, *J* = 2.1 Hz, 1H), 7.96 – 7.72 (m, 3H), 7.61 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.53 – 7.40 (m, 2H), 7.35 (td, *J* = 7.4, 1.3 Hz, 2H), 4.57 (d, *J* = 7.0 Hz, 2H), 4.31 (t, *J* = 7.0 Hz, 1H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 152.5, 143.3, 141.5, 139.0, 138.4, 135.4, 130.5, 128.2, 127.4, 125.1, 121.6,



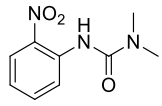
120.4, 116.7, 106.3, 68.7, 46.9. **HRMS-ESI** calcd. for $C_{22}H_{15}N_3O_4Na$ $(M+Na)^+$: 408.0955; Found: 408.0974.

(9*H*-Fluoren-9-yl)methyl(4-methoxy-2-nitrophenyl)carbamate (77). Compound **77**



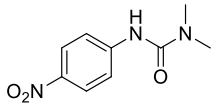
was prepared following the typical procedure G (16 h, 100 ºC) from Fmoc protected aniline **55** (69.12 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **77** as a dark yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 4:1); yield: 69.53 mg (89%); mp = 135-137 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 9.60 (bs, 1H, N*H*), 8.28 (d, *J* = 9.3 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.58 – 7.51 (m, 3H), 7.36 – 7.29 (t, *J* = 7.3 Hz, 2H), 7.25 (td, *J* = 7.4, 1.2 Hz, 2H), 7.11 (dd, *J* = 9.3, 3.0 Hz, 1H), 4.40 (d, *J* = 7.2 Hz, 2H), 4.20 (t, *J* = 7.2 Hz, 1H), 3.73 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 154.6, 153.2, 143.6, 141.4, 136.8, 128.9, 127.9, 127.3, 125.1, 123.8, 122.5, 120.2, 108.5, 67.8, 55.9, 47.0. **HRMS-ESI** calcd. for $C_{28}H_{18}N_2O_5Na$ $(M+Na)^+$: 413.1108; Found: 413.1099.

1,1-Dimethyl-3-(2-nitrophenyl)urea (*o*-20). Compound ***o*-20**, obtained together with



***p*-20**, was prepared following the typical procedure G (2 h, 50 ºC) from 1,1-dimethyl-3-phenylurea **12** (32.84 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give ***o*-20** as a pale yellow solid after purification through flash column chromatography (*n*-hexane/AcOEt 2:1); yield: 13.39 mg (32%); mp = 70-72 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.94 (s, 1H), 8.67 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.19 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.92 – 7.56 (m, 1H), 7.14 (ddd, *J* = 8.5, 7.2, 1.4 Hz, 1H), 3.09 (s, 6H). **HRMS-GC-EI** calcd. for $C_9H_{11}N_3O_3$ $(M)^+$: 209.0800; Found: 209.0804.

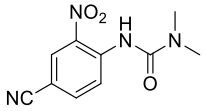
1,1-Dimethyl-3-(4-nitrophenyl) (*p*-20). Compound ***p*-20**, obtained together with



***o*-20**, was prepared following the typical procedure G (2 h, 50 ºC) from 1,1-dimethyl-3-phenylurea **12** (32.84 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give ***p*-20** as a pale yellow solid after purification through flash column chromatography

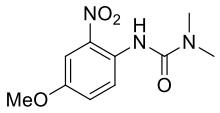
(*n*-hexane/AcOEt 2:1); yield: 17.99 mg (43%); mp = 206-208 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 8.37 (s, 1H), 8.20 – 8.02 (m, 2H), 7.93 – 7.58 (m, 2H), 3.04 (s, 6H). **^{13}C NMR (75 MHz, Acetone)** δ (ppm): 155.7, 148.3, 142.5, 125.3, 119.1, 36.6. **HRMS-ESI** calcd. for $C_9H_{12}N_3O_3$ $(M+H)^+$: 210.0873; found: 210.0868.

3-(4-Cyano-2-nitrophenyl)-1,1-dimethylurea (38). Compound **38**, was prepared



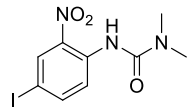
following the typical procedure G (10 min, 100 ºC) from 3-(4-cyanophenyl)-1,1-dimethylurea **29** (37.84 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **38** as a yellow after purification through flash column chromatography (*n*-Hexane/EtOAc 2:1); yield: 46.41 mg (99%); mp = 163-165 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 10.21 (s, 1H), 8.87 (dd, *J* = 9.0, 1.5 Hz, 1H), 8.62 (d, *J* = 2.1 Hz, 1H), 8.00 (dd, *J* = 9.0, 2.0 Hz, 1H), 3.11 (s, 6H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 154.4, 141.9, 138.6, 136.2, 131.3, 122.4, 117.9, 104.8, 36.5. **HRMS-GC-EI** calcd. for $C_{10}H_{10}N_4O_3$ $(M)^+$: 234.0753; Found: 234.0755.

3-(4-Methoxy-2-nitrophenyl)-1,1-dimethylurea (78). Compound **78** was prepared



following the typical procedure G (5 min, rt) from 3-(4-methoxyphenyl)-1,1-dimethylurea **56** (38.85 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **78** as a orange solid after purification through flash column chromatography (*n*-Hexane/EtOAc 3:1); yield: 43.12 mg (90%); mp = 115-117 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.64 (s, 1H), 8.53 (d, *J* = 9.4 Hz, 1H), 7.62 (d, *J* = 3.1 Hz, 1H), 7.31 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.87 (s, 3H), 3.06 (s, 6H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 155.4, 154.6, 137.6, 132.0, 124.2, 124.1, 108.6, 56.3, 36.3 **HRMS-GC-EI** calcd. for $C_{10}H_{13}N_3O_4$ (M^+): 239.0906; Found: 239.0904.

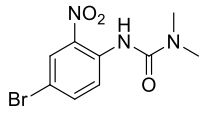
3-(4-Iodo-2-nitrophenyl)-1,1-dimethylurea (79). Compound **79** was prepared



following the typical procedure G (2 h, 50 ºC) from 3-(4-iodophenyl)-1,1-dimethylurea **57** (58.02 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **79** as a yellow solid after purification through flash column chromatography

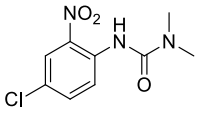
(*n*-Hexane/EtOAc 6:1); yield: 36.17 mg (54%); mp = 136-138 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.88 (s, 1H), 8.49 (d, *J* = 9.1 Hz, 1H), 8.45 (d, *J* = 2.1 Hz, 1H), 7.95 (dd, *J* = 9.1, 2.1 Hz, 1H), 3.08 (s, 6H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 154.7, 144.6, 138.2, 137.5, 134.4, 123.9, 82.2, 36.4. **HRMS-GC-EI** calcd. for $C_9H_{10}N_3O_3I$ $(M)^+$: 334.9767; Found: 334.9758.

3-(4-Bromo-2-nitrophenyl)-1,1-dimethylurea (80). Compound **80** was prepared



following the typical procedure G (2 h, 50 ºC) from 3-(4-bromophenyl)-1,1-dimethylurea **58** (48.62 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **80** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 6:1); yield: 35.01 mg (61%); mp = 101-103 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.88 (s, 1H), 8.64 (dd, *J* = 9.3, 1.4 Hz, 1H), 8.30 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.08 (s, 6H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 154.8, 138.9, 137.7, 137.3, 128.5, 123.8, 112.9, 36.4. **HRMS-GC-EI** calcd. for $C_9H_{10}N_3O_3Br$ $(M)^+$: 286.9906; Found: 286.9913.

3-(4-Chloro-2-nitrophenyl)-1,1-dimethylurea (81). Compound **81** was prepared



following the typical procedure G (2 h, 50 ºC) from 3-(4-chlorophenyl)-1,1-dimethylurea **59** (39.73 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **81** as a yellow solid. No further purification was required after $NaHCO_3$ extraction, yield: 36.45 mg (75%); mp = 87-89 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.88 (s, 1H), 8.70 (d, *J* = 9.3 Hz, 1H), 8.17 (d, *J* = 2.7 Hz, 1H), 7.69 (ddd, *J* = 9.3, 2.6, 0.5 Hz, 1H), 3.08 (s, 6H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm) 154.8, 137.3, 137.0, 136.1, 126.1, 125.6, 123.6, 36.4. **HRMS-GC-EI** calcd. for $C_9H_{10}N_3O_3Cl$ $(M)^+$: 243.0411; Found: 243.0400.

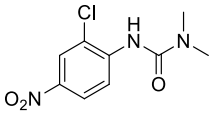
3-(4-Fluoro-2-nitrophenyl)-1,1-dimethylurea (82). Compound **82** was prepared following the typical procedure G (2 h, 50 ºC) from 3-(4-fluorophenyl)-1,1-dimethylurea **60** (36.44 mg, 0.2 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **82** as a yellow solid. No further purification was required after $NaHCO_3$ extraction, yield: 42.69 mg (94%); mp = 98-100 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 9.76 (s, 1H), 8.68 (dd, *J* = 9.5, 5.3 Hz, 1H), 7.93 (dd, *J* = 9.0, 3.1 Hz, 1H), 7.67 – 7.17 (m, 1H), 3.07 (s, 6H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 156.6 (d, J_{C-F} = 240.7 Hz), 155.0, 136.9 (d, J_{C-F} = 7.5 Hz), 135.1 (d, J_{C-F} = 2.2 Hz), 124.3 (d, J_{C-F} = 6.7 Hz), 123.8 (d, J_{C-F} = 22.5 Hz), 112.2 (d, J_{C-F} = 27.7 Hz), 36.4. **^{19}F NMR (282 MHz, Acetone-*d*$_6$)** δ (ppm): 55.7. **HRMS-ESI** calcd. for $C_9H_{11}N_3O_3F$ $(M+H)^+$: 228.0778; Found: 228.0780.

3-(2-Methoxy-4-nitrophenyl)-1,1-dimethylurea (105). Compound **105** was prepared following the typical procedure G (1.5 h at rt or 25 min at 50 ºC) from 3-(2-methoxyphenyl)-1,1-dimethylurea **99** (38.84 mg, 0.2 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **105** as a light yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 4:1); yield: 33.17 mg (85%); mp = 154-155ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.40 (d, *J* = 9.1 Hz, 1H), 7.90 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.71 (d, *J* = 2.5 Hz, 1H), 7.37 (s, 1H), 3.98 (s, 3H), 3.06 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 154.5, 146.8, 141.7, 135.7, 118.1, 116.9, 105.1, 56.5, 36.5. **HRMS-GC-EI** calcd. for $C_{10}H_{13}N_3O_4$ $(M)^+$: 239.0906; Found: 239.0917.

3-(2-Fluoro-4-nitrophenyl)-1,1-dimethylurea (106). Compound **106** was prepared following the typical procedure G (1 h, 50 ºC) from 3-(2-fluorophenyl)-1,1-dimethylurea **100** (36.44 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **106** as a light yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 6:1); yield: 37.71 mg (83%); mp = 170-172 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.47 (dd, *J* = 9.2, 7.9 Hz, 1H), 8.10 – 7.99 (m, 1H), 7.97 (dd, *J* = 11.1, 2.5 Hz, 1H), 6.90 (s, 1H), 3.08 (s, 6H). **^{13}C NMR (75 MHz,**

Chloroform-*d*) δ (ppm): 153.9, 150.5 (d, J_{C-F} = 243.0 Hz), 141.6 (d, J_{C-F} = 8.2 Hz), 134.6 (d, J_{C-F} = 9.0 Hz), 121.0 (d, J_{C-F} = 3.0 Hz), 119.4 (d, J_{C-F} = 2.2 Hz), 110.8 (d, J_{C-F} = 24.7 Hz), 36.7. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm) 49.0. **HRMS-ESI** calcd. for $C_9H_{11}N_3O_3F$ $(M+H)^+$: 228.0778; Found: 228.0782.

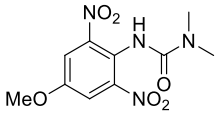
3-(2-Chloro-4-nitrophenyl)-1,1-dimethylurea (107). Compound **107** was prepared following the typical procedure G (6 h, 50 ºC) from 3-(2-chlorophenyl)-1,1-dimethylurea **101** (39.73 mg, 0.20 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **107** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 10:1); yield: 42.40 mg (87%); mp = 150-151ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.53 (d, *J* = 9.3 Hz, 1H), 8.25 (d, *J* = 2.6 Hz, 1H), 8.12 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.35 (s, 1H), 3.10 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 153.9, 142.0, 141.8, 124.7, 123.8, 121.3, 118.9, 36.6. **HRMS-GC-EI** calcd. for $C_9H_{10}N_3O_3Cl$ (M^+): 243.0411; Found: 243.0408.



4.2.3. Copper-catalyzed dinitration of protected anilines

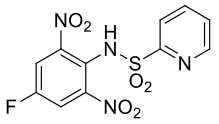
***Typical procedure H**:* A 20 mL vessel was charged with the corresponding *N*-protected aniline (0.20 mmol) and copper(II)nitrate (10-30 mol%). The reaction vessel was sealed with a Teflon lined aluminium cap, then evacuated and flushed with oxygen three times. Under the atmosphere of oxygen, acetonitrile (1.0 mL) and HNO_3 (26 µL, 0.40 mmol, 2.0 equiv) were added via syringe. The reaction was then heated at the corresponding temperature for the indicated time. When the reaction was finished, the mixture was diluted with EtOAc (5.0 mL) and washed twice with $NaHCO_3$ (sat.) reextracting next the aqueous phase with EtOAc (3 x 5.0 mL). The combined organic layers were then dried over $MgSO_4$ and filtered. The crude obtained after evaporation was purified by SiO_2 flash cromatography using the optimal *n*-Hexane/EtOAc mixture as eluent to provide the corresponding pure nitrocompound.

3-(4-Methoxy-2,6-dinitrophenyl)-1,1-dimethylurea (110). Compound **110** was



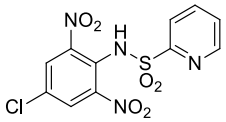
prepared following the typical procedure H [2 h, 50 ºC, 10% $Cu(NO_3)_2$] from 3-(4-methoxyphenyl)-1,1-dimethylurea **56** (38.84 mg, 0.20 mmol) and HNO_3 (26 µL, 0.20 mmol) to give **110** as a orange solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:1); yield: 46.12 mg (81%); mp = 158-160 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.63 (s, 1H), 7.85 (s, 2H), 4.01 (s, 3H), 3.02 (s, 6H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 155.6, 155.2, 146.1, 123.0, 116.1, 57.2, 36.5. **HRMS-ESI** calcd. for $C_{10}H_{13}N_4O_6$ $(M+H)^+$: 285.0829; Found: 285.0828.

***N*-(4-Fluoro-2,6-dinitrophenyl)pyridine-2-sulfonamide (111).** Compound **111** was



prepared following the typical procedure H [4 h, 100 ºC, 10% $Cu(NO_3)_2$] from sulfonylated aniline **43** (50.51 mg, 0.20 mmol) and HNO_3 (26 µL, 0.40 mmol) to give **111** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:4); yield: 49.92 mg (73%); mp = 174-178 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.36 (d, *J* = 4.5 Hz, 1H), 7.76 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 2H), 7.32 (ddd, *J* = 7.5, 4.8, 0.9 Hz, 1H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 162.5, 155.4 (d, $J_{C\text{-}F}$ = 245.4 Hz), 149.9, 149.30 (d, $J_{C\text{-}F}$ = 8.2 Hz), 138.9, 131.5 (d, $J_{C\text{-}F}$ = 3.5 Hz), 126.2, 121.3, 116.0 (d, $J_{C\text{-}F}$ = 27.0 Hz). **^{19}F NMR (282 MHz, Acetone-d_6)** δ (ppm): 57.9. **HRMS-ESI** calcd. for $C_{11}H_7N_4O_6S$ $(M+H)^+$: 343.0143; Found: 343.0154.

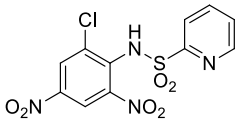
***N*-(4-Chloro-2,6-dinitrophenyl)pyridine-2-sulfonamide (112).** Compound **122** was



prepared following the typical procedure H [4 h, 100 ºC, 10% $Cu(NO_3)_2$] from sulfonylated aniline **42** (53.72 mg, 0.2 mmol) and HNO_3 (26 µL, 0.40 mmol) to give **122** as a dark yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:4); yield: 60.96 mg (85%); mp > 250 ºC (decomposition). **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.65 (d, *J* = 4.6 Hz, 1H), 8.00 – 7.89 (m, 3H), 7.68 – 7.59 (d, *J* = 7.8 Hz, 1H), 7.50 (ddd, *J* = 7.6, 5.0, 0.9 Hz, 1H). **^{13}C NMR**

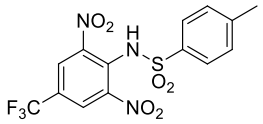
(75 MHz, Acetone-d_6) δ (ppm): 162.4, 149.8, 149.3, 139.5, 134.5, 127.8, 126.4, 124.4, 121.6. **HRMS-ESI** calcd. for $C_{11}H_7N_4O_6S$ $(M+H)^+$: 358.9853; Found: 358.9852.

***N*-(2-Chloro-4,6-dinitrophenyl)pyridine-2-sulfonamide (116).** Compound **116** was



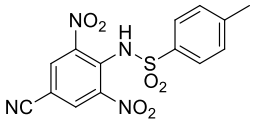
prepared following the typical procedure H [4 h, 100 ºC, 10% $Cu(NO_3)_2$] from sulfonylated aniline **96** (53.71 mg, 0.20 mmol) and HNO_3 (26 µL, 0.40 mmol) to give **116** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:4); yield: 41.65 mg (58%); mp = 128-132 ºC. **^{1}H RMN (300 MHz, Acetone-d_6)** δ (ppm): 8.52 (d, *J* = 4.8 Hz, 1H), 8.40 (d, *J* = 2.9 Hz, 1H), 8.21 (d, *J* = 2.9 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.48 – 7.24 (m, 1H). **^{13}C RMN (75 MHz, Acetone-d_6)** δ (ppm): 163.8, 149.4, 146.8, 145.0, 138.9, 137.7, 133.0, 127.3, 125.8, 121.3, 120.6. **HRMS-ESI** calcd. for $C_{11}H_7ClN_4O_6SNa$ $(M+Na)^+$: 380.9667; Found: 380.9669.

***N*-(2,6-Dinitro-4-(trifluoromethyl)phenyl)-*p*-toluenesulfonamide (113).** Compound



113 was prepared following the typical procedure H [24 h, 100 ºC, 30% $Cu(NO_3)_2$] from sulfonylated aniline **47** (63.18 mg, 0.20 mmol) and HNO_3 (26 µL, 0.40 mmol) to give **113** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:3); yield: 61.68 mg (76%); mp = >240 ºC decomposition. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.06 (d, *J* = 0.8 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.27 – 6.83 (m, 2H), 2.34 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 147.9, 144.7, 141.2, 140.0, 129.3, 126.6, 124.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.2 (q, $J_{C\text{-}F}$ = 267.7 Hz), 117.8 (q, $J_{C\text{-}F}$ = 27.0 Hz), 21.3. **^{19}F NMR (282 MHz, Acetone-d_6)** δ (ppm): 115.3. **HRMS-ESI** calcd. for $C_{14}H_9F_3N_3O_6S$ $(M-H)^-$: 404.0169; Found: 404.0183.

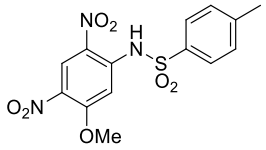
***N*-(4-Cyano-2,6-dinitrophenyl)-*p*-toluenesulfonamide (114).** Compound **114** was



prepared following the typical procedure H [24 h, 100 ºC, 30% $Cu(NO_3)_2$] from sulfonylated aniline **22** (54.55 mg, 0.20 mmol) and HNO_3 (28 µL, 0.44 mmol) to give **114** as a

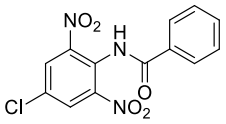
yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:3); yield: 56.53 mg (78%); mp = >260 ºC decomposition. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.05 (s, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.29 – 6.79 (m, 2H), 2.33 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 147.4, 145.4, 141.7, 140.8, 130.8, 129.2, 126.5, 117.9, 96.6, 21.2. **HRMS-ESI** calcd. for $C_{14}H_9N_4O_6S$ $(M-H)^-$: 361.0248; Found: 361.0256.

***N*-(5-Methoxy-2,4-dinitrophenyl)-4-methylbenzenesulfonamide (115).** Compound



115 was prepared following the typical procedure H [14 h, 100 ºC, 10% $Cu(NO_3)_2$] from sulfonylated aniline **86** (63.10 mg, 0.20 mmol) and HNO_3 (26 µL, 0.44 mmol) to give **115** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:3); yield: 60.92 mg (83%); mp = 167-169 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.37 (s, 1H), 8.78 (s, 1H), 8.18 – 7.84 (m, 2H), 7.55 – 7.34 (m, 3H), 4.08 (s, 3H), 2.42 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 158.7, 146.4, 140.8, 136.6, 134.0, 131.2, 129.4, 128.7, 126.2, 103.3, 58.2, 21.5. **HRMS-GC-EI** calcd. for $C_{14}H_{13}N_3O_7S$ (M^+): 367.0474; Found: 367.0477.

***N*-(4-Chloro-2,6-dinitrophenyl)benzamide (117).** Compound **117** was prepared



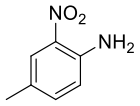
following the typical procedure (72 h, 100 ºC) from mononitrated compound **74** (55.32 mg, 0.2 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **117** as a yellow solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:1); yield: 46.35 mg (72%); mp = 200-202 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.34 (bs, 1H, N*H*), 8.49 (s, 2H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 7.4 Hz, 2H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 166.1, 146.6, 133.8, 133.6, 131.6, 130.6, 129.8, 128.6, 126.15. **HRMS-ESI** calcd. for $C_{13}H_8ClN_3O_5Na$ $(M+Na)^+$: 344.0045; Found: 344.0050.

4.2.4. Cleavage of different protecting groups

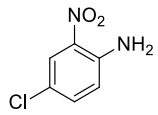
- ***Hydrolysis of nitrated anilines protected as benzanilides***[250]

To a round bottom flask containing a solution of KOH (25.0 mmol, 1.4 g) in MeOH (20 mL) was portionwise added the corresponding benzanilide (0.5 mmol). The resulting mixture was then stirred at room temperature for 12 h until complete hydrolysis of the starting material. The volatiles were next removed under vacuum, diluting the crude with EtOAc and extracting the solution with water. The organic phase was dried over $MgSO_4$ and evaporated. The desired aniline was purified by SiO_2 flash chromatography (*n*-Hexane/EtOAc 2:1).

4-Methyl-2-nitroaniline (118). Aniline **118** was obtained following the typical procedure from **73** (128.10 mg, 0.50 mmol) to give **118** as an orange solid; yield: 73.93 mg (97%); mp = 115-117 ºC (mp^{lit} = 116-117 ºC).[251] **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.86 (d, *J* = 1.9 Hz, 1H), 7.15 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 5.98 (bs, 2H, N*H*), 2.23 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 142.9, 137.3, 131.9, 126.6, 125.2, 118.9, 20.1. **HRMS-CG-EI** calcd. for $C_7H_8N_2O_2$ (M^+): 152.0586; Found: 152.0583.



4-Chloro-2-nitroaniline (119). Aniline **119** was obtained following the typical procedure from **74** (138.33 mg, 0.50 mmol) to give **119** as an orange solid; yield: 85.46 mg (99%); mp = 116-117 ºC (mp^{lit} = 113-115 ºC).[252] **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.01 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.68 (d, *J* = 8.9 Hz, 1H), 5.98 (bs, 2H, N*H*). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 143.3, 136.0, 132.2, 125.5, 121.7, 120.2. **HRMS-CG-EI** calcd. for $C_6H_5ClN_2O_2$ (M^+): 172.0040; Found: 172.0032.



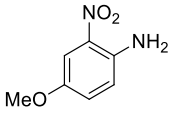
[250] T. Zhang, Y. Zhang, M. Luo, *Advanced Synthesis & Catalysis*, **2013**, *355*, 2775.

[251] J. H. Boyer, *Chem. Commun*. **1983,** *23*, 1388.

[252] T. E. Nickson, C. A. Roche-Dolson, *Synthesis*, **1985**, *7*, 669.

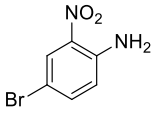
- ***Hydrolysis of nitrated anilines protected as ureas***[253]

4-Methoxy-2-nitroaniline (120). A suspension of 3-(4-methoxy-2-nitrophenyl)-1,1-dimethylurea **(78)** (135.02 mg, 0.56 mmol) in a saturated solution of KOH (10 mL) was refluxed for 3.5 h. After that time, the media was acidified until pH 5 and extracted with EtOAc (3 x 15 mL); the organic phase was dried over $MgSO_4$ and evaporated. The desired aniline was purified by SiO_2 flash chromatography (*n*-Hexane/EtOAc 1:2), phase yielding an orange solid; yield: 78.01 mg (83%); mp = 126-128 ºC (mp^{lit} = 120-122 ºC).[254] **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.15 (bs, 2H, N*H*), 7.52 (d, *J* = 3.1 Hz, 1H), 7.32 (dd, *J* = 9.2, 3.1 Hz, 1H), 7.13 (d, *J* = 9.2 Hz, 1H), 3.85 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 153.6, 150.2, 134.4, 127.4, 121.7, 107.0, 56.4.



- ***Deprotection of N-4-Nosyl nitrated anilines***[255]

4-Bromo-2-nitroaniline (121). In a round-bottomed flask is prepared a suspension of nosylated aniline **71** (40.32 mg, 0.10 mmol) and K_2CO_3 (55.33 mg, 0.40 mmol) in acetonitrile (2.0 mL) to which was added DMSO (50 µL) and PhSH (0.5 mmol, 51 µL). The mixture was then heated at 100ºC for 24h. When finished, the reaction was quenched and diluted with sat. NH_4Cl, and extracted with EtOAc (3 x 5.0 mL); the organic phase was dried over $MgSO_4$, filtered and evaporated. Deprotected aniline was then purified by SiO_2 flash chromatography using *n*-Hexane/EtOAc (4:1) as eluent; yielding **121**, 20.86 mg (96%) as an orange solid; mp = 110-112 ºC (mp^{lit} = 109-110 ºC).[256] **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.24 (d, *J* = 2.3 Hz, 1H), 7.41 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.73 (d, *J* = 8.9 Hz, 1H), 6.12 (bs, 2H, N*H*). **^{13}C NMR (75 MHz, Chloroform-*d*)**



[253] M. Hutchby, C. E. Houlden, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2009**, *48*, 8721,

[254] M-I. Makosza, M. Bia-Iecki, *J. Org. Chem.* **1998**, *63*, 4878.

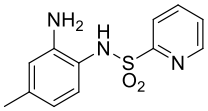
[255] M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J.-L. Peglion, E. Clot, O. Baudoinn, *J. Am. Chem. Soc.* **2008**, *130*, 15157.

[256] R. Heppolette, J. Miller, *J. Am. Chem. Soc.* **1953***, 75*, 4265.

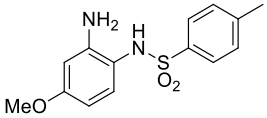
δ (ppm): 143.7, 138.46, 132.6, 128.4, 120.5, 107.9. **HRMS-GC-EI** calcd. for $C_6H_5BrN_2O_2$ (M^+): 215.9534; Found: 215.9532.

4.2.5. Reduction of the nitro group without cleavage of the sulfonamide protecting group

***N*-(2-Amino-4-methylphenyl)pyridine-2-sulfonamide (122).** To a closed round-bottomed flask containing the catalyst (10% Pd/C wet, 6.01 mg, 20% in weight) under inert atmosphere was added a solution of protected nitroaniline **4** (29.32 mg, 0.10 mmol) in MeOH (1.5 mL). Then, a ballon of H_2 was pierced through the septum and with the help of vacuum, reductive atmosphere was made inside. The set reaction was stirred at room temperature until consumption of starting material. When the reaction was completed, the flask was opened, the suspension filtered through a celite pad to remove the catalyst and the filtrate evaporated to dryness. The resulting crude was further purified by SiO_2 flash chromatography (*n*-Hexane/EtOAc 1:2) yielding **122** as a white solid; yield: 25.01 mg (95%); mp = 165-166 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.76 (d, *J* = 4.7 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.84 (td, *J* =7.6, 1.6 Hz, 1H), 7.50 (ddd, *J* = 7.4, 4.6, 1.4 Hz, 1H), 7.14 (bs, 1H, N*H*), 6.71 (d, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 1.7 Hz, 1H), 6.35 (dd, *J* = 8.0, 1.7 Hz, 1H), 4.22 (bs, 2H, N*H*), 2.16 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 157.1, 150.1, 143.9, 139.1, 138.3, 128.5, 127.1, 123.6, 119.7, 118.3, 117.6, 21.2. **HRMS-CG-EI** calcd. for $C_{12}H_{13}N_3O_2S$ (M^+): 263.0728; Found: 263.0735.



***N*-(4-Methoxyphenyl)-p-toluenesulfonamide (123).** Amino compound **123** was prepared following the typical procedure from nitrated aniline **67** (322 mg, 1.00 mmol) to give reduced compound **123** as a orange solid after purification through flash column chromatography (*n*-Hexane/EtOAc 1:2); yield: 254.3 mg (87%); mp = 118-120 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.59 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.63 (bs, 1H, NH), 6.32 (d, *J* = 8.7 Hz, 1H), 6.22 (d, *J* = 2.8 Hz, 1H), 6.01 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.18 (bs, 2H, NH), 3.65



(s, 3H), 2.37 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 160.2, 146.5, 143.8, 136.1, 130.3, 129.6, 127.7, 113.9, 104.3, 101.6, 55.3, 21.6.

4.2.6. Synthesis of benzo[*d*]imidazol-2(3*H*)-ones

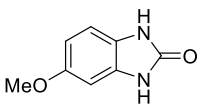
5-Methyl-1-(pyridin-2-ylsulfonyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (124). To a solution of (2-amino-4-methylphenyl)pyridine-2-sulfonamide **(122)** (500 mg, 1.90 mmol) in 20 mL of dry DCM under inert atmosphere was added, dropwise, at 0 ºC, a solution of triphosgene (620 mg, 2.09 mmol) in 15 mL of DCM. The reaction mixture was stirred at that temperature for 1 h, then it was carried to rt and stirred for another 5 h. After purification through flash column chromatography (*n*-Hexane/EtOAc 1:2), the desired product was isolated as a white solid (476 mg, 87%); mp = 190-192 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.10 (s, 1H), 8.63 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.28 – 8.14 (m, 2H), 7.74 (ddd, *J* = 7.4, 4.7, 1.4 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.00 – 6.95 (m, 1H), 6.93 (dd, *J* = 1.5, 0.8 Hz, 1H), 2.35 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 156.3, 151.8, 151.2, 139.5, 135.1, 129.7, 129.3, 126.9, 124.5, 123.5, 113.7, 111.1, 21.3. **HRMS-CG-EI** calcd. for $C_{13}H_{12}N_3O_3S$ $(M+H)^+$: 290.0593; Found: 290.0593.

5-Methoxy-1-(*p*-toluenesulfonyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (125). To a solution of *N*-(4-methoxyphenyl)-*p*-toluenesulfonamide **(123)** (43.02 mg, 0.15 mmol) in 1.0 mL of dry DCM under inert atmosphere was added, dropwise, at 0 ºC, a solution of triphosgene (47.71 mg, 0.16 mmol) in 1.5 mL of DCM. The reaction mixture was stirred at that temperature for 1 hour, then it was carried to rt and stirred for another 5 h. After purification through flash column chromatography (*n*-Hexane/EtOAc 1:2), the desired product was isolated as a white solid (41.42 mg, 89%); mp = 210-212 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 10.04 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.55 – 7.33 (m, 2H), 6.72 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 3.78 (s, 3H), 2.42 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 158.3, 151.9, 146.7, 136.3, 130.7, 130.7, 128.5,

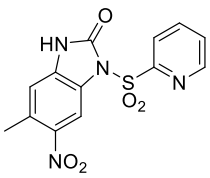
121.6, 114.4, 108.3, 97.2, 56.0, 21.5. **HRMS-CG-EI** calcd. for $C_{15}H_{15}N_2O_4S$ $(M+H)^+$: 319.0747; Found: 319.0744.

4.2.7. Deprotection of the sulfonyl group of 5-Methoxy-1-(*p*-toluenesulfonyl)-1*H*-benzo[*d*]imidazol-2(3*H*)-one (125)

5-Methoxy-1*H*-benzo[*d*]imidazol-2(3*H*)-one (126). To a solution of **125** (90.01 mg, 0.28 mmol) in MeOH (10 mL) were added Mg turnings (138.01 mg, 5.68 mmol). The reaction mixture was then stirred under sonication at rt for 1.5 h. After that time, the reaction mixture was filtered through a pad of Celite although the Mg was completely dissolved. The filtrate was then concentrated and it was dissolved in AcOEt (30 mL). After successively washes with a saturated aq. solution of K_2CO_3 (3 x 10 mL) and brine, the organic phase was concentrated to dryness. The residue was purified by flash chromatography (*n*-hexane-EtOAc + 5% MeOH 1:3, stained with ninhydrin) to afford **126** as a white solid; yield: 37.62 mg (81%); mp = 255-257 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 9.47 (s, 2H), 6.89 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.56 (ddd, *J* = 8.4, 2.5, 0.9 Hz, 1H), 3.75 (s, 3H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ (ppm): 155.6, 154.3, 130.5, 123.5, 108.7, 106.0, 95.3, 55.4. **HRMS-CG-EI$^+$**, calcd. for $C_8H_8N_2O_2$ $(M)^+$: 164.0586; Found: 164.0579.



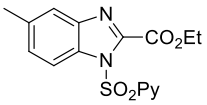
4.2.8. Nitration of 100; synthesis of 5-Methyl-6-nitro-1-(pyridin-2-ylsulfonyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (127)



Compound **127**, was prepared following the typical mononitration procedure (1 h, 100 ºC) from benzoimidazol-2(3*H*)one **124** (57.91 mg, 0.2 mmol) and HNO_3 (13 µL, 0.20 mmol) to give **127** as a yellow solid after purification through flash column chromatography (AcOEt) and crystallization (acetone); yield: 51.51 mg (77%); m.p. = 186-188 ºC. **^{1}H NMR (DMSO-d_6)** δ (ppm): 8.69 (d, *J* = 4.5 Hz, 1H), 8.32 (s, 1H), 8.31 – 8.19 (m, 2H), 7.81 (ddd, *J* = 6.2, 4.8, 1.2 Hz, 1H), 7.14 (s, 1H), 2.59 (s, 3H). **^{13}C NMR (DMSO-d_6)** δ (ppm): 153.9, 151.0, 150.8, 142.7,

139.5, 133.4, 132.0, 129.3, 125.7, 123.7, 112.9, 109.2, 20.6. **HRMS-ESI$^-$** calcd. for $C_{13}H_9N_4O_5S$ $(M-H)^-$: 333.0299; Found: 333.0309.

4.2.9. Synthesis of Ethyl 5-methyl-1-(pyridin-2-ylsulfonyl)-1H-benzo[*d*]imidazole-2-carboxylate (129)[257]



A solution of ethyl glyoxalate (77.3 µL, 0.38 mmol) in 3.0 mL of dry toluene was added dropwise to a mixture of anhydrous magnesium sulfate (137.22 mg, 1.14 mmol) and *N*-(2-amino-4-methylphenyl)pyridine-2-sulfonamide **122** (100.0 mg, 0.38 mmol) in dry toluene (5.0 mL) at room temperature. Then the mixture was stirred for 24 h. After the starting material was disappeared, the magnesium sulfate was filtered off, and the filtrate was concentrated under vacuum. To the crude mixture, $PdCl_2$ (6.57 mg, 0.04 mmol), K_2CO_3 (102.27 mg, 0.74 mmol) and $PhI(OAc)_2$ (238.35 mg, 0.74 mmol) were successively added and under nitrogen atmosphere 1.0 mL of dry toluene were added. The reaction mixture was stirred at room temperature for 18 h. Then the mixture was filtered over a celite pad, and the corresponding filtrate was concentrated under vacuum and purified by flash chromatography on silica gel (*n*-Hexane/EtOAc 3:1) providing the desired product **129** as a colourless oil; yield: 39.09 mg (52%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.70 – 8.54 (m, 1H), 8.26 (dt, *J* = 8.0, 1.0 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 8.00 (td, *J* = 7.8, 1.7 Hz, 1H), 7.60 (d, *J* = 1.7 Hz, 1H), 7.55 (ddd, *J* = 7.8, 4.7, 1.1 Hz, 1H), 7.35 (dd, *J* = 8.6, 1.7 Hz, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 159.4, 155.9, 150.4, 143.3, 141.6, 138.2, 135.7, 132.3, 129.1, 128.2, 123.3, 121.4, 114.7, 63.3, 21.6, 14.1. **HRMS-ESI** calcd. for $C_{16}H_{16}N_3O_4S$ $(M+H)^+$: 346.0856; Found: 346.0840.

[257] S. Fu, H. Jiang, Y. Deng, and W. Zeng, *Adv. Synth. Catal.* **2011**, *353*, 2795.

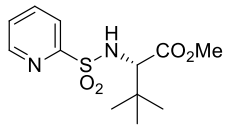
4.3. Palladium-catalyzed γ-C(sp^3)–H carbonylation of amino acid derivatives

All general reagents were obtained from usual commercial sources and were used, except when noted, without further purification. Amino acid derivatives were purchased from Aldrich Chemical Co., TCI and Bachem and used without further purification. Palladium(II) acetate, silver acetate and molybdenum hexacarbonyl were purchased from Aldrich Chemical Co. Benzoquinone was sublimated previously its use yielding a yellow powder.

4.3.1. Synthesis of *N*-(2-pyridyl)sulfonyl amino ester derivatives

Typical method I: *N*-(2-Pyridylsulfonyl) amino acids derivatives were prepared following a procedure described in the literature.[32] The appropriate amino acid hydrochloride ester derivative (3.30 mmol, 1.0 equiv) was weighed into a round bottom flask, then anhydrous MeCN (20 mL), (2-pyridyl)sulfonyl chloride (804 mg, 4.90 mmol, 1.5 equiv) and *N,N,N´,N´*-tetramethylethylenediamine (TMEDA) (2.90 mL, 20.00 mmol, 6.0 equiv) were successively added under argon. The mixture was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The crude was dissolved with EtOAc (20 mL), washed with 1 M HCl (aq.) (2 x 10 mL) and the aqueous phase was extracted with EtOAc (1 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified if necessary by trituration with diethylether or flash column chromatography (cyclohexane/EtOAc 2:1) to afford the corresponding *N*-(2-pyridyl)sulfonyl-amino acid derivative.

(*S*)-Methyl 3,3-dimethyl-2-(pyridine-2-sulfonamido)butanoate (130). Compound

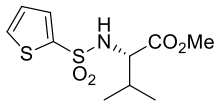


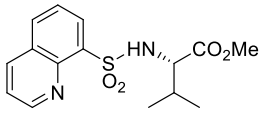
130 was prepared following the typical procedure I from *L*-tert-leucine methyl ester hydrochloride (600 mg, 3.30 mmol) to give **130** as a white solid; yield: 879 mg (93 %); mp = 121-123 ºC. **^{1}H NMR (300 MHz, Chloroform-d)** δ (ppm): 8.63 (d, *J* = 4.5 Hz, 1H), 8.00 – 7.93 (m, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.5, 4.7, 1.4 Hz, 1H), 5.40 (d, *J* = 10.2 Hz, 1H), 3.95 (d, *J* = 10.2 Hz,

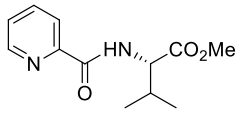
1H), 3.53 (s, 3H), 1.00 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-d)** δ (ppm): 171.3, 157.7, 149.7, 138.1, 126.7, 121.9, 65.2, 51.8, 34.7, 26.4. **HRMS-ESI** calcd. for $C_{12}H_{19}N_2O4S$ $(M+H)^+$: 287.1060; Found: 287.1061. **$[\alpha]_D^{25}$**: +27 (c = 1.0; CH_2Cl_2).

(*S*)-Methyl 3-methyl-2-(pyridine-2-sulfonamido)butanoate (132). Compound **132** was prepared following the typical procedure I from *L*-valine methyl ester hydrochloride (551 mg, 3.30 mmol) to give **132** as a white solid; yield: 870 mg (97%); mp = 108-109 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.63 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.96 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 5.33 (d, *J* = 9.6 Hz, 1H), 4.17 (dd, *J* = 9.7, 4.9 Hz, 1H), 3.58 (s, 3H), 2.23 – 1.88 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.8, 157.8, 149.7, 138.0, 126.7, 121.8, 62.1, 52.2, 31.7, 18.9, 17.4. **HRMS-ESI** calcd. for $C_{11}H_{17}N_2O_4S$ $(M+H)^+$: 273.0903; Found: 273.0914. $[\alpha]_D^{25}$: +17 (*c* = 1.0; CH_2Cl_2); ***ee*** = 99 %; **HPLC**: Daicel Chiralpak OJ, *i*-PrOH/hexane 2/98, flow rate 0.7 mL/min (λ= 254.4 nm), $\tau_{D,L}$: 80.7 min (*L*) and 88.5 min (*D*). IR (ν_{max}/cm^{-1}) 1740, 1581, 1453, 1344.

(*S*)-Methyl 3-methyl-2-(4-methylphenylsulfonamido)butanoate (134). Compound **134** was prepared following the typical procedure I from *L*-valine methyl ester hydrochloride (551 mg, 3.30 mmol) and tosyl chloride (935 mg, 4.90 mmol) to give **134** as a white solid; yield: 893 mg (95%); mp = 68-71 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.63 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.9 Hz, 2H), 5.04 (s, 1H), 3.66 (s, 1H), 3.37 (s, 3H), 2.34 (s, 3H), 1.95 (pd, *J* = 6.9, 5.3 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.8, 143.6, 136.7, 129.6, 127.3, 61.1, 52.2, 31.6, 21.5, 19.0, 17.6. **HRMS-ESI** calcd. for $C_{11}H_{20}NO_4S$ $(M+H)^+$: 287.1113; Found: 287.1118. **$[\alpha]_D^{25}$**: -9 (*c* = 1.0; CH_2Cl_2).

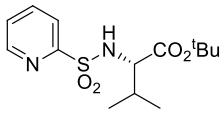
(S)-Methyl 3-methyl-2-(thiophene-2-sulfonamido)butanoate (135). Compound **135**  was prepared following the typical procedure I from *L*-valine methyl ester hydrochloride (551 mg, 3.30 mmol) and 2-thiophenylsulfonyl chloride (904 mg, 4.90 mmol) to give **135** as a light yellow solid; yield: 787 mg (86%); mp = 119-121 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.57 (m, 2H), 7.06 (ddd, *J* = 4.8, 3.7, 0.8 Hz, 1H), 5.21 (d, *J* = 10.0 Hz, 1H), 3.85 (dd, *J* = 10.0, 4.9 Hz, 1H), 3.53 (s, 3H), 2.06 (ddd, *J* = 13.7, 6.9, 5.2 Hz, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.7, 140.6, 132.6, 132.3, 127.4, 61.4, 52.5, 31.6, 19.0, 17.5. **HRMS-GC-EI** calcd. for $C_{10}H_{15}NO_4S_2$ $(M)^+$: 277.0443; Found: 277.0441. **$[\alpha]_D^{25}$**: +25 (*c* = 1.0; CH_2Cl_2).

(*S*)-Methyl 3-methyl-2-(quinoline-7-sulfonamido)butanoate (136). Compound **136**  was prepared following the typical procedure I from *L*-valine methyl ester hydrochloride (551 mg, 3.30 mmol) and 8-quinolinenylsulfonyl chloride (1.11 g, 4.90 mmol) to give **136** as a136 light yellow solid; yield: 936 mg (88%); mp = 114-115 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 9.09 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.36 (dd, *J* = 7.3, 1.5 Hz, 1H), 8.27 (dd, *J* = 8.4, 1.7 Hz, 1H), 8.04 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.68 – 7.50 (m, 2H), 6.78 (d, *J* = 9.4 Hz, 1H), 3.98 (dd, *J* = 9.3, 5.7 Hz, 1H), 3.06 (s, 3H), 2.15 – 1.93 (m, 1H), 0.96 (d, *J* = 2.0 Hz, 3H), 0.94 (d, *J* = 2.0 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.2, 151.1, 143.3, 136.9, 136.8, 133.3, 130.2, 128.7, 125.5, 122.3, 62.2, 51.4, 31.8, 18.9, 17.9. **HRMS-ESI** calcd. for $C_{15}H_{19}N_2O_4S$ $(M+H)^+$: 323.1060; Found: 323.1053. **$[\alpha]_D^{25}$**: +148 (*c* = 1.0; CH_2Cl_2).

(*S*)-Methyl 3-methyl-2-(picolinamido)butanoate (137). A 50 mL round-bottomed  flask immersed in a 0 °C bath (ice and water) was charged with picolinic acid (616 mg, 5.00 mmol) and CH_2Cl_2 (10 mL). To the stirred suspension was added oxalyl chloride (0.47 mL, 5.50 mmol) dropwise over a 15 minute period followed by addition of DMF (0.1 mL, catalytic amount) in one portion, producing a rust-red color and the evolution of a gas. The mixture was kept in the cooling bath for 1 h and then

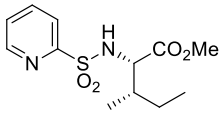
allowed to warm to room temperature. After gas evolution ceased, the mixture was again cooled to 0 °C. To this solution were successively added, *L*-valine methyl ester hydrochloride (922 mg, 5.50 mmol) and *N,N,N´,N´*-tetramethylethylenediamine (4.80 mL, 33.00 mmol).The brown mixture was left in the cooling bath for 30 minutes and then allowed to warm to room temperature. Stirring was continued at room temperature overnight. Removal of solvent in vacuo gave the crude product as a brown solid that was extracted with H_2O/EtOAc. The organic phases were combined and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (cyclohexane/EtOAc 2:1) to give **137** as a yellow oil; yield: 850 mg (72%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.58 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.54 – 8.43 (m, 1H), 8.16 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 4.72 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.75 (s, 3H), 2.30 (pd, *J* = 6.9, 5.1 Hz, 1H), 1.02 (d, *J* = 2.9 Hz, 3H), 1.00 (d, *J* = 2.9 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 172.1, 164.2, 149.4, 148.2, 137.3, 126.3, 122.2, 57.3, 52.1, 31.4, 19.1, 17.9. **HRMS-GC-EI** calcd. for $C_{12}H_{16}N_2O_3$ $(M)^+$: 236.1161; Found: 236.1158. **$[\alpha]_D^{25}$**: +16 (*c* = 1.0; CH_2Cl_2).

(*S*)-*tert*-Butyl 3-methyl-2-(pyridine-2-sulfonamido)butanoate (138). Compound



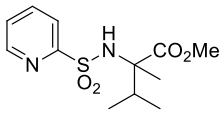
138 was prepared following the typical procedure I from *L*-valine *tert*-butyl ester hydrochloride (315 mg, 1.50 mmol) to give **138** as a light yellow solid; yield: 368 mg (78%); mp = 110-111 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.68 – 8.54 (m, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.88 (td, *J* = 7.7, 1.8 Hz, 1H), 7.45 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 5.30 (d, *J* = 9.3 Hz, 1H), 4.07 (dd, *J* = 9.3, 4.3 Hz, 1H), 2.12 (td, *J* = 7.0, 4.5 Hz, 1H), 1.32 (s, 9H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.4, 158.1, 149.9, 138.1, 126.6, 121.9, 82.1, 62.2, 31.8, 27.9, 19.1, 17.0. **HRMS-ESI** calcd. for $C_{14}H_{23}N_2O_4S$ $(M+H)^+$: 315.1373; Found: 315.1388. **$[\alpha]_D^{25}$**: +26 (*c* = 1.0; CH_2Cl_2).

(2*S*,3*S*)-Methyl 3-methyl-2-(pyridine-2-sulfonamido)pentanoate (139). Compound



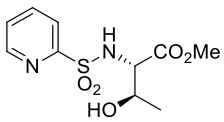
139 was prepared following the typical procedure I from *L*-isoleucine methyl ester hydrochloride (500 mg, 2.75 mmol) to give **139** as a white solid; yield: 662 mg (84%); mp = 97-99 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.63 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.01 – 7.91 (m, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 5.37 (d, *J* = 9.6 Hz, 1H), 4.19 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.56 (s, 3H), 1.84 (ddt, *J* = 9.4, 7.0, 4.8 Hz, 1H), 1.44 (ddd, *J* = 15.5, 7.4, 3.8 Hz, 1H), 1.18 (ddd, *J* = 13.6, 9.1, 7.0 Hz, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.8, 157.8, 149.7, 138.0, 126.7, 121.8, 61.3, 52.1, 38.5, 24.6, 15.4, 11.3. **HRMS-ESI** calcd. for $C_{12}H_{19}N_2O_4S$ $(M+H)^+$: 287.1066; Found: 287.1066. **$[\alpha]_D^{25}$**: +20 (*c* = 1.0; CH_2Cl_2).

Methyl 2,3-dimethyl-2-(pyridine-2-sulfonamido)butanoate (140). Compound **140**



was prepared following the typical procedure I from 2-methyl-*DL*-valine methyl ester hydrochloride (600 mg, 3.30 mmol) to give **140** as a white solid; yield: 537 mg (57%); mp = 125-128 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.69 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.02 – 7.95 (m, 1H), 7.89 (td, *J* = 7.7, 1.8 Hz, 1H), 7.47 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 5.46 (s, 1H), 3.62 (s, 3H), 2.03 (p, *J* = 6.8 Hz, 1H), 1.40 (s, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 173.6, 159.1, 149.9, 138.1, 126.5, 121.7, 66.0, 52.5, 37.2, 17.4, 17.0, 16.9. **HRMS-ESI** calcd. for $C_{12}H_{19}N_2O_4S$ $(M+H)^+$: 287.1066; Found: 287.1061.

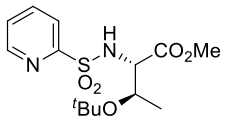
(2*S*,3*R*)-Methyl-3-hydroxy-2-(pyridine-2-sulfonamido)butanoate (141). Compound



141 was prepared following the typical procedure I from *L*-threonine methyl ester hydrochloride (500 mg, 2.95 mmol) to give **141** as a white solid; yield: 566 mg (70%); mp = 108-110 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.65 (ddd, *J* = 4.6, 1.8, 0.9 Hz, 1H), 7.97 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.56 – 7.39 (m, 1H), 6.28 (d, *J* = 9.4 Hz, 1H), 4.44 – 3.99 (m, 2H), 3.58

(s, 3H), 2.69 (s, 1H), 1.30 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.9, 157.8, 149.8, 138.3, 126.9, 121.8, 68.4, 62.2, 52.6, 19.9. **HRMS-ESI** calcd. for $C_{10}H_{15}N_2O_5S$ $(M+H)^+$: 275.0696; Found: 275.0703 **$[\alpha]_D^{25}$**: -12 (*c* = 1.0; CH_2Cl_2).

(2*S*,3*R*)-Methyl-3-(*tert*-butoxy)-2-(pyridine-2-sulfonamido)butanoate (142).



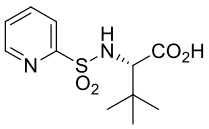
Compound **142** was prepared following the typical procedure I from *O*-*tert*-butyl-*L*-threonine methyl ester hydrochloride (744 mg, 3.30 mmol) to give **142** as a white solid; yield: 1.01 g (93 %); mp = 118-120 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.64 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 7.98 – 7.94 (m, 1H), 7.88 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H), 5.49 (d, *J* = 10.2 Hz, 1H), 4.21 (dd, *J* = 10.2, 1.9 Hz, 1H), 4.14 (qd, *J* = 6.2, 1.9 Hz, 1H), 3.53 (s, 3H), 1.27 (d, *J* = 6.2 Hz, 3H), 1.06 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.8, 158.2, 149.6, 137.9, 126.5, 121.5, 74.1, 67.9, 62.5, 52.1, 28.2, 20.7. **HRMS-ESI** calcd. For $C_{14}H_{23}N_2O_5S$ $(M+H)^+$: 331.1312, found: 331.1308. **$[\alpha]_D^{25}$**: -17 (*c* = 1.0; CH_2Cl_2).

4.3.2. Hydrolysis of *N*-(2-pyridyl)sulfonyl amino ester derivatives and synthesis of peptides[216]

Typical procedure J (ester hydrolysis): To a solution of the corresponding *N*-(2-pyridyl)sulfonyl amino ester (1.39 mmol, 1.00 equiv) in THF/H_2O/MeOH (1.2/0.4/0.4 mL)[258] was added $LiOH{\cdot}H_2O$ (175 mg, 4.17 mmol, 3.00 equiv) and the solution was stirred at the specified temperature over 24 hours. After this time, 1 M HCl (aq.) was added until pH 2 and a white solid precipitated. This solid was dissolved in EtOAc (20 mL) and the organic phase was extracted with HCl (1 x 7 mL) and water (1 x 7 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the corresponding *N*-(2-pyridyl)sulfonyl amino acids (**146** and **177**) as white solids, which were purified by simple trituration with pentane and diethylether.

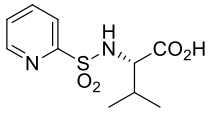
[258] The solution is 2 M respect to the $LiOH{\cdot}H_2O$.

(*S*)-3,3-Dimethyl-2-(pyridine-2-sulfonamido)butanoic acid (146). Compound **146**



was prepared following the typical procedure J (60 ºC, 24 h), from (*S*)-Methyl-3,3-dimethyl-2-(pyridine-2-sulfonamido) butanoate (**130**) (400 mg, 1.39 mmol) to give **146** as a white solid; yield: 352 mg (93%); mp = 194-196 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.63 (ddd, *J* = 4.7, 1.8, 1.0 Hz, 1H), 8.04 (td, *J* = 7.7, 1.8 Hz, 1H), 8.00 – 7.89 (m, 1H), 7.60 (ddd, *J* = 7.6, 4.7, 1.3 Hz, 1H), 6.48 (s, 1H), 3.94 (s 1H), 1.04 (s, 9H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 172.2, 159.5, 150.5, 139.1, 127.6, 122.3, 66.0, 34.9, 27.0. **HRMS-ESI** calcd. for $C_{11}H_{17}N_2O_4S$ $(M+H)^+$: 273.0903; Found: 273.0903. **$[\alpha]_D^{25}$**: +25 (*c* = 1.0; acetone).

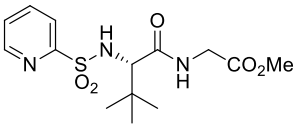
***(S)*-3-Methyl-2-(pyridine-2-sulfonamido)butanoic acid (174).** Compound **174** was



prepared following the typical procedure J (rt, 24 h), from (*S*)-methyl 3-methyl-2-(pyridine-2-sulfonamido)butanoate (**132**) (379 mg, 1.39 mmol) to give **174** as a white solid; yield: 327 mg (91%); mp = 118-120 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 11.24 (s, 1H), 8.59 (d, *J* = 4.7 Hz, 1H), 8.08 – 7.78 (m, 2H), 7.60 – 7.29 (m, 1H), 6.11 (d, *J* = 9.5 Hz, 1H), 4.10 (dd, *J* = 9.5, 4.6 Hz, 1H), 2.52 – 1.92 (m, 1H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 173.0, 159.4, 150.5, 139.1, 127.6, 122.2, 62.7, 32.0, 19.5, 17.8. **HRMS-ESI** calcd. for $C_{10}H_{15}N_2O_4S$ $(M+H)^+$: 259.0747; Found: 259.0745. **$[\alpha]_D^{25}$**: +16 (*c* = 0.5; acetone).

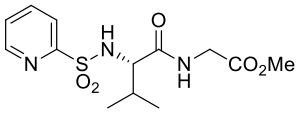
Typical procedure K (synthesis of dipeptides):[228] **146** or **174** (0.73 mmol, 1.0 equiv), HOBt·H_2O (109 mg, 0.81 mmol, 1.0 equiv), EDC·HCl (155 mg, 0.81 mmol, 1.0 equiv) and glycine methyl ester hydrochloride (93.2 mg, 0.73 mmol, 1.0 equiv) were suspended in anhydrous DCM (3.7 mL). Et_3N (0.20 mL, 1.47 mmol, 2.0 equiv) was added and the solution was stirred at room temperature 24 hours. The reaction mixture was then diluted with EtOAc (20 mL), transferred to a separatory funnel and sequentially washed with 0.5 M citric acid (aq.) (4 x 8 mL) and with saturated $NaHCO_3$ (1 x 8 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (cyclohexane/EtOAc 1:1 to 1:3) to obtain the desired peptides.

(*S*)-Methyl 2-[3,3-dimethyl-2-(pyridine-2-sulfonamido)butanamido]acetate (175).



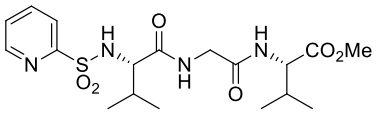
Compound **178** was prepared following the typical procedure K, from (*S*)-3,3-dimethyl-2-(pyridine-2-sulfonamido)butanoic acid (**146**) (200 mg, 0.73 mmol) to give **175** as a white solid; yield: 150 mg (60%); mp = 153-155 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.61 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.96 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.44 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 6.19 (s, 1H), 5.61 (d, *J* = 9.0 Hz, 1H), 3.94 (dd, *J* = 18.3, 5.3 Hz, 1H), 3.87 – 3.76 (m, 2H), 3.75 (s, 3H), 1.02 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.1, 169.8, 158.0, 149.9, 138.2, 126.8, 122.1, 66.1, 52.6, 41.3, 34.9, 26.7. **HRMS-ESI** calcd. for $C_{14}H_{22}N_3O_5S$ $(M+H)^+$: 344.1274; Found: 344.1277. **$[\alpha]_D^{25}$**: +34 (*c* = 0.7; acetone).

(*S*)-Methyl-2-[3-methyl-2-(pyridine-2-sulfonamido)butanamido]acetate (176).



Compound **179** was prepared following the typical procedure K, from *(S)*-3-methyl-2-(pyridine-2-sulfonamido)butanoic acid (**174**) (200 mg, 0.73 mmol) to give **176** as a white solid; yield: 163 mg (68%); mp = 118-120 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.67 (d, *J* = 4.8 Hz, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.88 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.14 (t, *J* = 5.5 Hz, 1H), 6.17 (s, 1H), 3.91 (m, 3H), 3.69 (s, 3H), 2.24 – 2.02 (m, 1H), 0.88 (m, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.2, 170.1, 157.5, 150.0, 138.3, 126.9, 122.4, 63.0, 52.4, 41.2, 31.4, 19.2, 17.3. **HRMS-ESI** calcd. for $C_{13}H_{20}N_3O_5S$ $(M+H)^+$: 330.1124; Found: 330.1125. **$[\alpha]_D^{25}$**: +12 (*c* = 1.0; CH_2Cl_2).

(*S*)-Methyl-3-methyl-2-{2-[(*S*)-3-methyl-2-(pyridine-2-sulfonamido)butanamido] acetamido}butanoate (180).

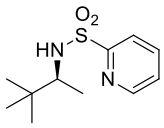


Compound **180** was prepared following the typical procedures J and K, from (*S*)-Methyl 2-(3-methyl-2-(pyridine-2-sulfonamido)butanamido)acetate (**176**) (236 mg, 0.75 mmol) to give **180** as a white solid; yield: 129 mg (40% for two steps); mp = 220-222 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.64 (d, *J* = 4.4 Hz,

1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H), 7.50 – 7.32 (m, 2H), 7.07 (d, *J* = 8.6 Hz, 1H), 6.22 (d, *J* = 8.2 Hz, 1H), 4.49 (dd, *J* = 8.6, 5.2 Hz, 1H), 3.92 (m, 3H), 3.73 (s, 3H), 2.14 (td, *J* = 7.2, 3.3 Hz, 2H), 0.89 (m, 12H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 172.3, 171.7, 168.8, 157.6, 150.1, 138.2, 127.0, 122.3, 63.1, 57.5, 52.4, 43.4, 31.4, 31.2, 19.3, 19.0, 18.0, 17.6. **HRMS-ESI** calcd. for $C_{18}H_{28}N_4NaO_6S$ $(M+Na)^+$: 451.1627; Found: 451.1631. **$[\alpha]_D^{25}$**: +8 (*c* = 0.14; CH_2Cl_2).

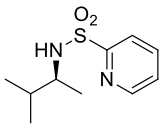
4.3.3. Synthesis of *N*-(2-pyridyl)sulfonyl amino derivatives

(*S*)-*N*-(3,3-Dimethylbutan-2-yl)pyridine-2-sulfonamide (148). Compound **148** was



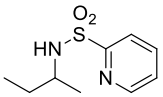
prepared following the typical procedure I from (*S*)-(+)-(3,3-dimethyl-2-butylamine) (1.0 mL, 7.34 mmol, 1.0 equiv) to give **148** as a white solid after column chromatography (cyclohexane/EtOAc 3:1); yield: 1.39 g (78%); mp = 117-119 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.71 (ddd, *J* = 4.8, 1.7, 0.8 Hz, 1H), 8.10 – 7.96 (m, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 4.74 (d, *J* = 9.7 Hz, 1H), 3.21 (dq, *J* = 9.5, 6.8 Hz, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 158.4, 150.0, 138.0, 126.5, 122.0, 58.9, 34.6, 26.2, 16.6. **HRMS-ESI** calcd. for $C_{11}H_{19}N_2O_2S$ $(M+H)^+$: 243.1161; Found: 243.1167 **$[\alpha]_D^{25}$**: -20 (*c* = 0.5; CH_2Cl_2).

(*S*)-*N*-(3-Methylbutan-2-yl)pyridine-2-sulfonamide (151). Compound **151** was



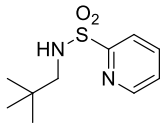
prepared following the typical procedure I from (*S*)-3-methylbutan-2-amine (1.0 mL, 8.56 mmol, 1.0 eq.) to give **151** as a white solid after column chromatography (cyclohexane/EtOAc 3:1); yield: 1.64 g (84%); mp = 72-74 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.69 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.89 (td, *J* = 7.8, 1.8 Hz, 1H), 7.67 – 7.41 (m, 1H), 4.93 (d, *J* = 8.5 Hz, 1H), 3.29 (dqd, *J* = 8.3, 6.7, 5.0 Hz, 1H), 1.66 (pd, *J* = 6.9, 5.1 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.83 (s, 3H), 0.81 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 158.2, 149.8, 138.0, 126.5, 121.9, 55.4, 33.4, 18.1, 17.9, 17.8. **HRMS-ESI** calcd. for $C_{10}H_{17}N_2O_2S$ $(M+H)^+$: 229.1011; Found: 229.1013 **$[\alpha]_D^{25}$**: -10 (*c* = 0.5; CH_2Cl_2).

***N*-(*Sec*-butyl)pyridine-2-sulfonamide (152).** Compound **152** was prepared following



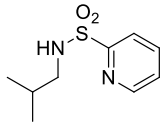
the typical procedure I from butan-2-amine (0.50 mL, 4.89 mmol) to give **152** as a white solid after column chromatography (cyclohexane/EtOAc 3:1); yield: 901 mg (86%); mp = 71-73 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.71 (ddt, *J* = 3.8, 1.8, 1.0 Hz, 1H), 8.01 (dq, *J* = 7.8, 1.0 Hz, 1H), 7.90 (tt, *J* = 7.8, 1.5 Hz, 1H), 7.60 – 7.37 (m, 1H), 4.92 (d, *J* = 7.9 Hz, 1H), 3.95 – 3.07 (m, 1H), 1.60 – 1.18 (m, 2H), 1.03 (dd, *J* = 6.6, 1.0 Hz, 3H), 0.82 (td, *J* = 7.4, 1.0 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 158.5, 150.1, 138.1, 126.6, 122.1, 52.1, 30.4, 21.2, 10.0. **HRMS-ESI** calcd. for $C_9H_{15}N_2O_2S$ $(M+H)^+$: 215.0848; Found: 215.0841.

***N*-Neopentylpyridine-2-sulfonamide (153).** Compound **153** was prepared following

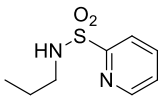


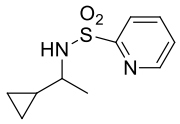
the typical procedure I from 2,2-dimethylpropan-1-amine (500 mg, 5.74 mmol) to give **153** as a white solid after column chromatography (cyclohexane/EtOAc 3:1); yield: 1.18 g (90%); mp = 68-70 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.71 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 4.89 (t, *J* = 6.0 Hz, 1H), 2.76 (d, *J* = 6.9 Hz, 2H), 0.91 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 157.6, 150.0, 138.1, 126.6, 122.2, 55.2, 31.6, 27.0. **HRMS-ESI** calcd. for $C_{10}H_{17}N_2O_2S$ $(M+H)^+$: 229.1005; Found: 229.1005.

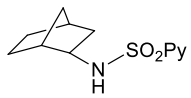
***N*-Isobutylpyridine-2-sulfonamide (154).** Compound **154** was prepared following



the typical procedure I from 2-methylpropan-1-amine (1.0 mL, 10.06 mmol) to give **154** as a colourless oil after column chromatography (cyclohexane/EtOAc 3:1); yield: 2.00 g (93%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.69 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 7.99 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.8, 1.3 Hz, 1H), 5.37 (t, *J* = 6.6 Hz, 1H), 2.82 (t, *J* = 6.6 Hz, 2H), 1.72 (dp, *J* = 13.4, 6.7 Hz, 1H), 0.88 (s, 3H), 0.85 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 157.2, 149.7, 138.0, 126.5, 122.1, 50.7, 28.4, 19.6. **HRMS-ESI** calcd. for $C_9H_{15}N_2O_2S$ $(M+H)^+$: 215.0854; Found: 215.0855.

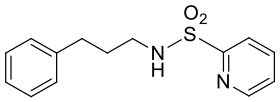
***N*-Propylpyridine-2-sulfonamide (155).** Compound **155** was prepared following the typical procedure I from propylamine (0.50 mL, 6.08 mmol) to give **155** as a white solid after column chromatography (cyclohexane/EtOAc 3:1); yield: 990 mg (81%); mp = 54-56 ºC. 
^{1}H NMR (300 MHz, Chloroform-*d*) δ (ppm): 8.69 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 8.00 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.49 (ddd, *J* = 7.6, 4.7, 1.3 Hz, 1H), 5.58 (t, *J* = 6.3 Hz, 1H), 2.97 (td, *J* = 7.2, 6.2 Hz, 2H), 1.48 (q, *J* = 7.3 Hz, 2H), 0.84 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 157.3, 149.9, 138.1, 126.6, 122.3, 45.2, 23.0, 11.0. **HRMS-ESI** calcd. for $C_8H_{13}N_2O_2S$ $(M+H)^+$: 201.0692; Found: 201.0686.

***N*-(1-Cyclopropylethyl)pyridine-2-sulfonamide (161).** Compound **161** was prepared following the typical procedure I from 1-cyclopropylethanamine hydrochloride (150 mg, 1.23 mmol) to give **161** as a white solid after column chromatography (cyclohexane/EtOAc 3:1 to 1:1); yield: 220 mg (79%); 
mp = 73-75 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.71 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.01 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 5.17 (d, *J* = 6.9 Hz, 1H), 2.79 (dp, *J* = 8.5, 6.7 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.77 (qt, *J* = 8.3, 4.9 Hz, 1H), 0.43 (dddd, *J* = 10.6, 5.9, 4.4, 3.0 Hz, 1H), 0.30 – 0.17 (m, 1H), 0.17 – 0.04 (m, 2H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 158.7, 150.0, 138.0, 126.6, 122.1, 55.6, 21.4, 18.1, 4.0, 3.4. **HRMS-ESI** calcd. for $C_{10}H_{13}N_2O_2S$ $(M-H)^-$: 225.0698; Found: 225.0699.

***N*-Bicyclo[2.2.1]heptan-2-yl-pyridine-2-sulfonamide (165).** Compound **165** was prepared following the typical procedure I from bicyclo[2,2,1]heptan-2-amine (1.00 g, 8.99 mmol, 1.0 equiv) using pyridine as base (4.30 mL, 53.9 mmol, 6.0 equiv) to give **165** as a white solid after column chromatography (cyclohexane/EtOAc 3:1 to 1:1); yield: 1.83 g (81%); mp = 126-127 ºC. 
^{1}H-NMR (300 MHz, Chloroform-*d*) δ (ppm): 8.72 (d, *J* = 3.9 Hz, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.91 (t, *J* = 7.7 Hz, 1H), 7.49 (dd, *J* = 7.5, 4.8 Hz, 1H), 4.92 (d, *J* = 6.8 Hz, 1H), 3.23 (dd, *J* = 8.8, 5.9 Hz, 1H), 2.16 (d, *J* = 24.8

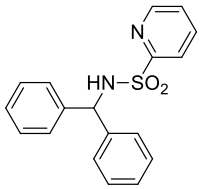
Hz, 2H), 1.65 – 1.52 (m, 1H), 1.41 (ddd, *J* = 18.4, 14.6, 8.0 Hz, 3H), 1.23 (d, *J* = 13.1 Hz, 1H), 1.12 (d, *J* = 10.2 Hz, 1H), 1.08 – 0.93 (m, 2H). **^{13}C-NMR (75 MHz, Chloroform-*d*)** δ (ppm): 158.1, 150.1, 138.1, 126.6, 122.3, 57.2, 42.8, 40.8, 35.7, 35.2, 28.1, 26.4. **HRMS-ESI** calcd. For $C_{12}H_{17}N_2O_2S$ $(M+H)^+$: 253.1005; Found: 253.1002.

***N*-(3-Phenylpropyl)pyridine-2-sulfonamide (166).** Compound **166** was prepared



following the typical procedure I from 3-phenylpropylamine (0.5 mL, 3.52 mmol) to give **166** as a white solid after column chromatography (cyclohexane/EtOAc 3:1 to 1:1); yield: 856 mg (88%); mp = 77-79 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.73 (ddd, *J* = 4.7, 1.8, 1.0 Hz, 1H), 8.03 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.93 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 7.37 – 7.22 (m, 2H), 7.26 – 7.17 (m, 1H), 7.21 – 7.08 (m, 2H), 5.20 – 5.05 (m, 1H), 3.11 (q, *J* = 6.8 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.06 – 1.74 (m, 2H). **^{13}C NMR (75 MHz Chloroform-*d*)** δ (ppm): 157.3, 149.9, 141.0, 138.1, 128.3, 128.3, 126.7, 125.9, 122.3, 43.0, 32.5, 31.3. **HRMS-ESI** calcd. for $C_{14}H_{17}N_2O_2S$ $(M+H)^+$: 277.1005; Found: 277.1009.

***N*-Benzhydrylpyridine-2-sulfonamide (168).** Compound **168** was prepared

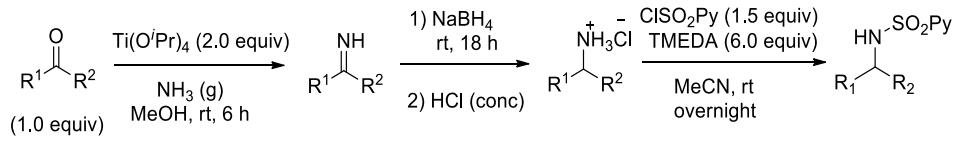


following the typical procedure I from benzhydralamine (1.5 mL, 8.70 mmol) to give **168** as a white solid after column chromatography (cyclohexane/EtOAc 3:1 to 1:1); yield: 2.50 g (89%); mp = 182-184 ºC. **^{1}H NMR (300 MHz, DMSO-d_6)** δ (ppm): 9.07 (d, *J* = 9.1 Hz, 1H), 8.47 (dt, *J* = 4.8, 1.3 Hz, 1H), 8.01 – 7.73 (m, 2H), 7.43 (ddd, *J* = 6.7, 4.7, 2.3 Hz, 1H), 7.35 – 7.05 (m, 10H), 5.72 (d, *J* = 8.9 Hz, 1H). **^{13}C NMR (75 MHz, DMSO-d_6)** δ (ppm): 157.8, 149.5, 141.6, 138.0, 128.0, 127.1, 126.8, 126.4, 121.5, 60.9. **HRMS-ESI** calcd. for $C_{18}H_{17}N_2O_2S$ $(M+H)^+$: 325.1011; Found: 325.1009.

***N*-(2-Methyl-1-phenylpropyl)pyridine-2-sulfonamide (169).** Compound **169** was prepared following the typical procedure I from 2-methyl-1-phenylpropan-1-amine (100.1 mg, 0.67 mmol) to give **169** as a white solid after column chromatography (cyclohexane/EtOAc 3:1 to 1:1); yield: 153.7 mg (79%); mp = 103-104ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.39 (ddd, *J* = 4.7, 1.8, 1.0 Hz, 1H), 7.64 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.57 (td, *J* = 7.7, 1.8 Hz, 1H), 7.22 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 7.04 – 6.95 (m, 3H), 6.92 (dq, *J* = 5.8, 1.5 Hz, 2H), 5.86 (d, *J* = 9.0 Hz, 1H), 4.11 (dd, *J* = 9.0, 8.0 Hz, 1H), 2.12 – 1.79 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (75 MHz Chloroform-*d*)** δ (ppm): 157.7, 149.6, 139.7, 137.4, 128.0, 127.2, 127.0, 126.0, 122.0, 64.9, 34.3, 19.5, 19.3. **HRMS-ESI** calcd. for $C_{15}H_{19}N_2O_2S$ $(M+H)^+$: 291.1161; Found: 291.1162.

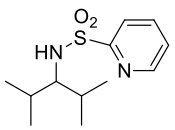
***N*-Phenethylpyridine-2-sulfonamide (172).** Compound **172** was prepared following the typical procedure I from phenethylamine (0.491 mL, 3.90 mmol, 1.0 equiv) using pyridine as base (43.51 mL, 23.4 mmol, 6.0 equiv) to give **172** as a white solid after column chromatography (cyclohexane/EtOAc 3:1); yield: 1.09 g (98%); mp = 90-92 ºC. **^{1}H-RMN (300 MHz, Chloroform-*d*)** δ (ppm): 8.62 (d, *J* = 4.6 Hz, 1H), 8.02 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.91 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.35 – 7.19 (m, 3H), 7.18 – 7.06 (m, 2H), 5.68 (t, *J* = 5.6 Hz, 1H), 3.34 (dd, *J* = 13.6, 7.0 Hz, 2H), 2.83 (t, *J* = 7.2 Hz, 2H). **^{13}C-RMN (75 MHz, Chloroform-*d*)** δ (ppm): 157.4, 150.1, 138.1, 138.0, 128.9, 128.7, 126.7, 122.3, 44.8, 36.2. **HRMS-ESI** calcd. for $C_{13}H_{15}N_2O_2S$ $(M+H)^+$: 263.0848; Found: 263.0856.

4.3.4. Synthesis of *N*-(2-pyridyl)sulfonyl amino derivatives from the corresponding ketones



Typical procedure L: The corresponding ketone (10.00 mmol) was dissolved in 25 mL of dry methanol and titanium(IV) isopropoxide (6.0 mL, 20.00 mmol) was added. Then NH_3 (g) was bubbled for 15 min and the solution was stirred at room temperature for 6 h. The mixture was placed in a cooling bath at 0 ºC and sodium borohydride (600 mg, 15.00 mmol) was added in portions. The resulting solution was kept at 0 ºC for 15 min and then warmed up to room temperature. The mixture was stirred overnight. The reaction was quenched by pouring into 2 M ammonium hydroxide (25 mL). The resulting inorganic white precipitate was filtered and washed with EtOAc (4 x 25 mL). The combined organic phases were dried over $MgSO_4$, filtered over celite and the solvent was concentrated to the half under reduced pressure.[259] The resulting organic phase was extracted with concentrated HCl (4 x 10 mL). The acidic aqueous phases were combined and washed with diethylether (3 x 10 mL) in order to remove organic impurities. The aqueous phase was concentrated under reduced pressure yielding the corresponding aminohydrochloride salts.[260] Following procedure I the desired *N*-(2-pyridyl)sulfonyl amino derivatives were synthesized.

***N*-(2,4-Dimethylpentan-3-yl)pyridine-2-sulfonamide (159).** Compound **159** was



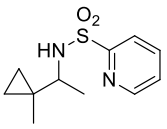
prepared following the typical procedure L from 2,4-dimethyl-3-pentanone (1.42 mL, 10.00 mmol) to give **159** as a white solid after column chromatography (cyclohexane/EtOAc 4:1 to 2:1); yield: 1.35 g (53% for three steps); mp = 165-167 ºC. **^{1}H NMR (300 MHz,**

[259] Important Note: These alkyl amines are very volatiles. Do not heat the rotavap bath.

[260] Important Note: Caution, HCl(g) is generated.

Chloroform-*d*) δ (ppm): 8.71 (dt, *J* = 4.7, 1.2 Hz, 1H), 7.97 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.87 (td, *J* = 7.7, 1.8 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.7, 1.3 Hz, 1H), 4.57 (d, *J* = 9.9 Hz, 1H), 3.05 (dt, *J* = 9.9, 5.9 Hz, 1H), 1.76 (dq, *J* = 13.3, 6.7 Hz, 2H), 0.77 (dd, *J* = 6.8, 1.4 Hz, 12H). **^{13}C NMR (75 MHz Chloroform-*d*)** δ (ppm): 159.0, 149.9, 137.8, 126.3, 121.5, 66.0, 30.2, 20.5, 17.8. **HRMS-ESI** calcd. for $C_{12}H_{21}N_2O_2S$ $(M+H)^+$: 257.1318; Found: 257.1318.

***N*-(1-(1-Methylcyclopropyl)ethyl)pyridine-2-sulfonamide (162).** Compound **162** was prepared following the typical procedure L from methyl 1-methylcyclopropyl ketone (1.10 mL, 10.00 mmol) to give **162** as a white solid after column chromatography (cyclohexane/EtOAc 2:1 to 1:1); yield: 913 mg (38% for three steps); mp = 95-97 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.68 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.99 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.88 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 5.16 (d, *J* = 7.4 Hz, 1H), 2.79 (p, *J* = 6.9 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 3H), 0.35 – 0.13 (m, 3H), 0.11 – 0.01 (m, 1H). **^{13}C NMR (75 MHz Chloroform-*d*)** δ (ppm): 158.5, 150.0, 137.9, 126.5, 122.0, 58.0, 20.3, 18.9, 17.7, 13.4, 11.9. **HRMS-ESI** calcd. for $C_{11}H_{17}N_2O_2S$ $(M+H)^+$: 241.1005; Found: 257.1011.



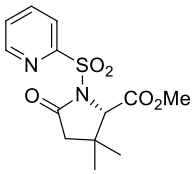
4.3.5. Palladium-catalyzed carbonylation protocol

Typical procedure M: An oven dried Ace Pressure tube with Teflon stir bar was charged with the corresponding *N*-(2-pyridyl)sulfonyl-protected amino derivative (0.104 mmol, 1.0 equiv), silver(I) acetate (26.04 mg, 0.156 mmol, 1.5 equiv), benzoquinone (22.48 mg, 0.208 mmol, 2.0 equiv), molybdenumhexacarbonyl (9.06 mg, 0.034 mmol, 0.33 equiv), palladium(II) acetate (2.33 mg, 0.010 mmol) and 0.2 mL of 1,1,1,3,3,3-hexafluoro-2-propanol. The pressure tube was then sealed with a screw-cap and the reaction was placed in a preheated oil bath at 110 ºC over 18 h. At this point, the reaction mixture was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was then diluted with EtOAc, filtered through a pad of Celite and concentrated under reduced pressure. The residue was

purified by flash column chromatography using mixtures of cyclohexane:EtOAc, indicated for each example, affording the corresponding carbonylation compounds.

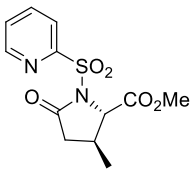
- ***Carbonylation of amino acid derivatives***

(*S*)-Methyl-3,3-dimethyl-5-oxo-1-(pyridin-2-ylsulfonyl)pyrrolidine-2-carboxylate



(131). Compound **131** was prepared following the typical procedure M from **130** (29.78 mg, 0.104 mmol) to give **131** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 6:1 to 3:1); yield: 26.96 mg (83%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.69 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.25 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.97 (td, *J* = 7.8, 1.7 Hz, 1H), 7.56 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 4.63 (s, 1H), 3.83 (s, 3H), 2.62 (d, *J* = 16.8 Hz, 1H), 2.13 (d, *J* = 16.8 Hz, 1H), 1.27 (s, 3H), 1.13 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 172.6, 170.0, 155.9, 150.1, 138.2, 128.0, 124.4, 70.5, 52.7, 45.3, 37.4, 29.0, 23.7. **HRMS-ESI** calcd. for $C_{13}H_{17}N_2O_5S$ $(M+H)^+$: 313.0852; Found: 313.0851. **$[\alpha]_D^{25}$**: +5 (*c* = 0.2; CH_2Cl_2). **IR** (ν_{max}/cm^{-1}) 1757, 1740, 1579, 1349. Compound **131** was also prepared following procedure M on a 3.50-mmol scale, using **130** (1.00 g, 3.50 mmol), silver(I) acetate (874 mg, 5.23 mmol), benzoquinone (759 mg, 0.21 mmol), molybdenumhexacarbonyl (305 mg, 1.15 mmol), palladium(II) acetate (78.58 mg, 0.35 mmol) and 6.7 mL of 1,1,1,3,3,3-hexafluoro-2-propanol. The reaction mixture was stirred at 110 ºC for 24 hours. The title compound **131** was isolated in 77 % yield (842 mg).

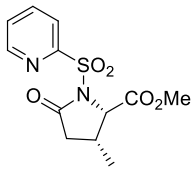
(2*S*,3*S*)-Methyl-3-methyl-5-oxo-1-(pyridin-2-ylsulfonyl)pyrrolidine-2-carboxylate



(*trans*-133). Compound *trans*-**133** (together with *cis*-**133**) was prepared following the typical procedure M from **132** (28.31 mg, 0.104 mmol) to give *trans*-**133** as a white solid after flash column chromatography (cyclohexane/EtOAc 6:1 to 3:1); yield: 23.27 mg (75%), *cis*/*trans* = 15:85; mp = 123-125 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.76 – 8.54 (m, 1H), 8.39 – 8.09 (m, 1H), 7.93 (td, *J* = 7.8, 1.8 Hz, 1H), 7.53 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 4.60 (d, *J* = 3.0 Hz, 1H), 3.78 (s,

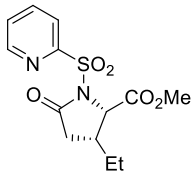
3H), 2.76 (dd, *J* = 17.2, 8.2 Hz, 1H), 2.53 (ddd, *J* = 7.7, 5.7, 3.4 Hz, 1H), 2.01 (dd, *J* = 17.3, 3.5 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H). **75 MHz, Chloroform-*d*)** δ (ppm): 172.7, 170.6, 155.6, 150.0, 138.2, 127.9, 124.2, 67.4, 52.9, 38.6, 32.0, 20.2. **HRMS-ESI** calcd. for $C_{12}H_{15}N_2O_5S$ $(M+H)^+$: 299.0696; Found: 299.0699. **$[\alpha]_D^{25}$**: -10 (*c* = 0.5; CH_2Cl_2). ***ee* = 97 %**; HPLC: Daicel Chiralpak IA, MeOH/CO_2 3/97, flow rate 0.7 mL/min (λ= 254.4 nm), τ : 12.4 min (2*S,* 3*S-trans*), 13.2 (2*R,* 3*R-trans*), 16.4 (2*S,* 3*R-cis*) min. **IR** (ν_{max}/cm^{-1}) 1763, 1746, 1577, 1437, 1361. Compound *trans*-**133** was also prepared following procedure E on a 1.80-mmol scale, using **132** (500 mg, 1.80 mmol), silver(I) acetate (451 mg, 2.70 mmol), benzoquinone (389 mg, 3.60 mmol), molybdenumhexacarbonyl (157 mg, 0.59 mmol), palladium(II) acetate (40.41 mg, 0.18 mmol) and 3.5 mL of 1,1,1,3,3,3-hexafluoro-2-propanol. The reaction mixture was stirred at 110 ºC for 24 hours. The title compound *trans*-**133** was isolated in 70 % yield (376 mg), *cis*/*trans* = 15:85.

(2*S*,3*R*)-Methyl-3-methyl-5-oxo-1-(pyridin-2-ylsulfonyl)pyrrolidine-2-carboxylate



(*cis*-133). Compound *cis*-**133** (together with *trans*-**133**) was prepared following the typical procedure M from **132** (28.31 mg, 0.104 mmol) to give *cis*-**133** as a colourless oil after flash column chromatography (cyclohexane/EtOAc 6:1 to 3:1); yield: 1.55 mg (5%) (*cis*-configuration determined by NOE correlation). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.69 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.25 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.96 (td, *J* = 7.8, 1.7 Hz, 1H), 7.55 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 4.99 (d, *J* = 8.5 Hz, 1H), 3.83 (s, 3H), 2.94 – 2.73 (m, 1H), 2.60 – 2.27 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 3H). **HRMS-ESI** calcd. for $C_{12}H_{15}N_2O_5S$ $(M+H)^+$: 299.0696; Found: 299.0699.

(2*S*,3*R*)-Methyl-3-ethyl-5-oxo-1-(pyridin-2-ylsulfonyl)pyrrolidine-2-carboxylate



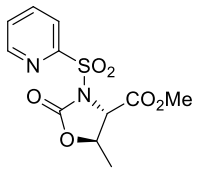
(143). Compound **143** was prepared following the typical procedure M from **139** (29.78 mg, 0.104 mmol) to give **143** as a colourless oil after flash column chromatography (cyclohexane/EtOAc 6:1 to 3:1); yield: 15.59 mg (48%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.69 (d, *J* = 4.9 Hz, 1H), 8.25

(dd, *J* = 7.9, 1.1 Hz, 1H), 7.96 (td, *J* = 7.8, 1.8 Hz, 1H), 7.55 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 5.02 (d, *J* = 8.2 Hz, 1H), 3.81 (s, 3H), 2.73 – 2.54 (m, 1H), 2.53 – 2.33 (m, 2H), 1.27 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 172.8, 169.7, 155.7, 150.1, 138.2, 127.9, 124.5, 64.0, 52.6, 38.6, 36.6, 23.5, 12.1. **HRMS-ESI** calcd. for $C_{13}H_{17}N_2O_5S$ $(M+H)^+$: 313.0852; Found: 313.0851. **$[\alpha]_D^{25}$**: -25 (*c* = 0.5; CH_2Cl_2).

***trans*-Methyl-2,3-dimethyl-5-oxo-1-(pyridin-2-ylsulfonyl)pyrrolidine-2-carboxylate (*trans*-144).** Compound *trans*-**144** (together with *cis*-**144**, *cis*/*trans* = 40:60) was prepared following the typical procedure M from **140** (29.78 mg, 0.104 mmol) to give *trans*-**144** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 6:1 to 4:1); yield: 16.24 mg (50%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.68 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.26 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.94 (td, *J* = 7.8, 1.7 Hz, 1H), 7.52 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 3.88 (s, 3H), 2.83 – 2.64 (m, 1H), 2.55 (dd, *J* = 17.0, 7.9 Hz, 1H), 2.17 (dd, *J* = 17.0, 11.8 Hz, 1H), 1.78 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 172.6, 172.2, 155.7, 149.9, 137.9, 127.6, 125.1, 71.6, 53.3, 37.8, 37.3, 17.0, 14.0. **HRMS-ESI** calcd. for $C_{13}H_{17}N_2O_5S$ $(M+H)^+$: 313.0852; Found: 313.0848. **IR** (ν_{max}/cm^{-1}) 1733, 1582, 1458, 1419, 1345.

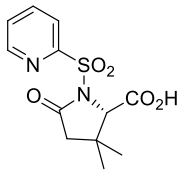
***cis*-Methyl-2,3-dimethyl-5-oxo-1-(pyridin-2-ylsulfonyl)pyrrolidine-2-carboxylate (*cis*-144).** Compound *cis*-**144** (together with *trans*-**144**, *cis*/*trans* = 40:60) was prepared following the typical procedure M from **140** (29.78 mg, 0.104 mmol) to give *cis*-**144** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 6:1 to 4:1); yield: 12.02 mg (37%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.71 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.28 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.95 (td, *J* = 7.8, 1.7 Hz, 1H), 7.53 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 3.86 (s, 3H), 2.62 – 2.20 (m, 3H), 1.94 (s, 3H), 1.05 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 173.7, 171.2, 156.1, 150.0, 138.0, 127.6, 124.8, 72.3, 52.9, 39.4, 37.9, 23.6, 14.6. **HRMS-ESI** calcd. for $C_{13}H_{17}N_2O_5S$ $(M+H)^+$: 313.0852; Found: 313.0850.

(*4S*,5*R*)-Methyl-5-methyl-2-oxo-3-(pyridin-2-ylsulfonyl)oxazolidine-4-carboxylate



(145). Compound **145** was prepared following the typical procedure M from **141** (28.53 mg, 0.104 mmol) to give **145** as a white solid after flash column chromatography (cyclohexane/EtOAc 6:1 to 3:1); yield: 26.54 mg (85%); mp = 92-94 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.70 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.21 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.99 (td, *J* = 7.8, 1.7 Hz, 1H), 7.59 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 4.85 (d, *J* = 4.9 Hz, 1H), 4.67 (qd, *J* = 6.3, 4.9 Hz, 1H), 3.88 (s, 3H), 1.60 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 168.6, 155.3, 151.0, 150.3, 138.5, 128.4, 124.6, 75.1, 64.9, 53.6, 21.1. **HRMS-ESI** calcd. for $C_{11}H_{13}N_2O_6S$ $(M+H)^+$: 301.0488; Found: 301.0481. **$[\alpha]_D^{25}$**: -73 (*c* = 0.2; CH_2Cl_2). **IR** (ν_{max}/cm^{-1}) 1801, 1794, 1755, 1580, 1429, 1375.

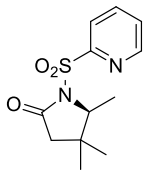
(*S*)-3,3-Dimethyl-5-oxo-1-(pyridin-2-ylsulfonyl)pyrrolidine-2-carboxylic acid



(147). Compound **147** was prepared following the typical procedure M from **146** (28.32 mg, 0.104 mmol). The reaction crude was disolved with EtOAc (20 mL) and extracted with 1 M $NaHCO_3$ (3 x 10 mL). The combined aqueous phases were washed with diethyl ether (2 x 10 mL) and acidified to pH 2. The solution was then extracted with EtOAc (3 x 12 mL). The combined organic phases were dried over $MgSO_4$ and solvent was evaporated under reduced pressure affording the desired product **147**as a brownish solid; yield: 25.13 mg (81%); mp = 75-77 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.75 (dt, *J* = 4.7, 1.4 Hz, 1H), 8.33 – 8.08 (m, 2H), 7.76 (p, *J* = 4.3 Hz, 1H), 4.55 (s, 1H), 2.60 (d, *J* = 16.7 Hz, 1H), 2.14 (d, *J* = 16.7 Hz, 1H), 1.29 (s, 3H), 1.21 (s, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 173.0, 171.0, 157.1, 151.1, 139.4, 129.0, 124.5, 71.3, 45.5, 37.6, 28.9, 23.9. **HRMS-ESI** calcd. for $C_{12}H_{15}N_2O_5S$ $(M+H)^+$: 299.0696; Found: 299.0696. **$[\alpha]_D^{25}$**: +12 (*c* = 0.2; Acetone). **IR** (ν_{max}/cm^{-1}) 3672-2453, 1756, 1699, 1583, 1375.

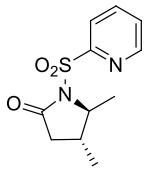
- ***Carbonylation of aliphatic amines***

(*S*)-4,4,5-Trimethyl-1-(pyridin-2-ylsulfonyl)pyrrolidin-2-one (149). Compound **149**



was prepared following the typical procedure M from **148** (25.20 mg, 0.104 mmol) to give **149** as a brownish solid after flash column chromatography (cyclohexane/EtOAc 6:1 to 3:1); yield: 24.84 mg (89%); mp = 124-126 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.62 (ddd, *J* = 4.7, 1.7, 0.8 Hz, 1H), 8.18 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.88 (td, *J* = 7.8, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 4.12 (q, *J* = 6.6 Hz, 1H), 2.38 (d, *J* = 17.0 Hz, 1H), 1.97 (d, *J* = 16.9 Hz, 1H), 1.41 (d, *J* = 6.7 Hz, 3H), 1.09 (s, 3H), 1.03 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ 173.1, 155.7, 149.9, 138.0, 127.6, 124.4, 66.5, 44.6, 37.0, 28.4, 22.8, 17.6. **HRMS-ESI** calcd. for $C_{12}H_{17}N_2O_3S$ $(M+H)^+$: 269.0954; Found: 269.0954. **$[\alpha]_D^{25}$**: +17 (*c* = 0.5; CH_2Cl_2). **IR** (ν_{max}/cm^{-1}) 1744, 1580, 1422, 1344. Compound **149** was also prepared following procedure M on a 4.10-mmol scale, using **148** (1.00 g, 4.10 mmol), silver(I) acetate (1.03 g, 6.15 mmol), benzoquinone (886 mg, 8.20 mmol), molybdenumhexacarbonyl (357 mg, 1.35 mmol), palladium(II) acetate (92.05 mg, 0.41 mmol) and 7.9 mL of 1,1,1,3,3,3-hexafluoro-2-propanol. The reaction mixture was stirred at 110 ºC for 24 hours. The title compound **149** was isolated in 85% yield (935 mg).

(4*R*,5*S*)-4,5-Dimethyl-1-(pyridin-2-ylsulfonyl)pyrrolidin-2-one (156). Compound



156 was prepared following the typical procedure M from **151** (23.74 mg, 0.104 mmol) to give **156** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 6:1 to 2:1); yield: 20.63 mg (78%), *cis*/*trans* = 15:85. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.82 – 8.47 (m, 1H), 8.29 – 8.15 (m, 1H), 7.95 (td, *J* = 7.8, 1.8 Hz, 1H), 7.53 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 4.23 (qd, *J* = 6.4, 2.4 Hz, 1H), 2.76 (dd, *J* = 17.4, 7.8 Hz, 1H), 2.11 (tdd, *J* = 9.7, 7.4, 3.8 Hz, 1H), 1.99 (dd, *J* = 17.3, 3.1 Hz, 1H), 1.58 (d, *J* = 6.4 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 173.7, 156.2, 150.1, 138.0, 127.6, 124.5, 64.6, 38.6, 34.8, 21.7, 20.0. **HRMS-ESI** calcd. for $C_{11}H_{15}N_2O_3S$ $(M+H)^+$: 255.0797; Found: 255.0794. **$[\alpha]_D^{25}$**: +11 (*c* = 0.5; CH_2Cl_2). **IR** (ν_{max}/cm^{-1}) 1751, 1580, 1453, 1419, 1344.

4,4-Dimethyl-1-(pyridin-2-ylsulfonyl)pyrrolidin-2-one (157). Compound **157** was prepared following the typical procedure M [20 mol% $Pd(OAc)_2$] from **153** (23.74 mg, 0.104 mmol) to give **157** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 6:1 to 3:1); yield: 18.78 mg (71%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.63 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.14 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.89 (td, *J* = 7.8, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 3.79 (s, 2H), 2.23 (s, 2H), 1.15 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 173.6, 156.2, 150.2, 138.2, 127.7, 124.2, 60.7, 47.1, 33.8, 26.9. **HRMS-ESI** calcd. for $C_{11}H_{15}N_2O_3S$ $(M+H)^+$: 255.0797; Found: 255.0793. **IR** (ν_{max}/cm^{-1}) 1757, 1578, 1437, 1359.

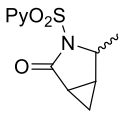
4-Methyl-1-(pyridin-2-ylsulfonyl)pyrrolidin-2-one (158). Compound **158** was prepared following the typical procedure M [20 mol% $Pd(OAc)_2$] from **154** (22.28 mg, 0.104 mmol) to give **158** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 6:1 to 3:1); yield: 10.49 mg (42%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.69 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.19 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.96 (td, *J* = 7.8, 1.7 Hz, 1H), 7.54 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 4.35 – 4.03 (m, 1H), 3.71 (dd, *J* = 9.8, 6.5 Hz, 1H), 2.78 – 2.38 (m, 2H), 2.34 – 1.88 (m, 1H), 1.18 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 173.8, 156.2, 150.2, 138.2, 127.7, 124.2, 55.4, 40.4, 27.4, 18.9. **HRMS-ESI** calcd. for $C_{10}H_{13}N_2O_3S$ $(M+H)^+$: 241.0641; Found: 241.0641. **IR** (ν_{max}/cm^{-1}) 1748, 1579, 1445, 1419, 1358.

***trans*-5-Isopropyl-4-methyl-1-(pyridin-2-ylsulfonyl)pyrrolidin-2-one (*trans*-160).** Compound *trans*-**160** was prepared following the typical procedure M from **159** (26.66 mg, 0.104 mmol) to give *trans*-**160** as a white solid after flash column chromatography (cyclohexane/EtOAc 6:1 to 2:1); yield: 20.85 mg (71%) (*trans*-diastereoselective); mp = 110-111 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.68 (d, *J* = 4.5 Hz, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 7.95 (td, *J* = 7.8, 1.8 Hz, 1H), 7.53 (ddd, *J* = 7.6, 4.6, 1.2 Hz, 1H), 4.06 (d, *J* = 4.1 Hz, 1H), 2.71 (dd, *J* = 18.0, 8.7 Hz, 1H), 2.62 – 2.45 (m, 1H), 2.32 (p, *J* = 7.4 Hz, 1H), 1.93 (dd, *J* = 18.0, 1.3 Hz, 1H), 1.18 (d, *J* = 7.1 Hz, 3H), 1.06

(d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 174.4, 156.2, 150.0, 138.0, 127.6, 124.9, 73.7, 39.9, 32.4, 27.2, 22.7, 19.0, 16.1. **HRMS-ESI** calcd. for $C_{13}H_{19}N_2O_3S$ $(M+H)^+$: 283.1110; Found: 283.1114. **IR** (ν_{max}/cm^{-1}) 1732, 1625, 1576, 1360.

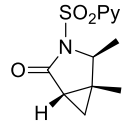
- ***Carbonylation of cyclopropylmethylamine derivatives***

4-Methyl-3-(pyridin-2-ylsulfonyl)-3-azabicyclo[3.1.0]hexan-2-one (163).



Compound **163**, obtained as an inseparable 50:50 mixture of *cis*/*trans* diastereoisomers, was prepared following the typical procedure M from **161** (22.26 mg, 0.104 mmol) and $Pd(OAc)_2$ (30 mol%) to give **163** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 4:1); yield: 15.10 mg (60%). **^{1}H RMN (300 MHz, Chloroform-*d*,** one of the diastereoisomers) δ (ppm): 8.68 (d, *J* = 4.5 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.02 – 7.82 (m, 1H), 7.52 (dd, *J* = 7.5, 4.7 Hz, 1H), 4.51 (dd, *J* = 12.2, 5.9 Hz, 1H), 2.00 – 1.84 (m, 1H), 1.77 (dt, *J* = 10.4, 5.2 Hz, 1H), 1.64 (d, *J* = 6.3 Hz, 3H), 1.22 – 1.06 (m, 1H), 0.94 (dd, *J* = 8.1, 4.6 Hz, 1H). **^{13}C RMN (75 MHz,** one of the diastereoisomers) δ (ppm): 173.2, 156.0, 150.0, 138.1, 127.6, 124.5, 58.6, 23.4, 20.4, 19.8, 12.3. **HRMS-ESI** calcd. for $C_{11}H_{12}N_2O_3S$ $(M+H)^+$: 253.0641; Found: 253.0641. **IR** (ν_{max}/cm^{-1}): 1739, 1513, 1471.

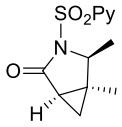
***cis*-4,5-Dimethyl-3-(pyridin-2-ylsulfonyl)-3-azabicyclo[3.1.0]hexan-2-one (*cis*-164).**



Compound *cis*-**164**, obtained together with *trans*-**164**, (*cis*/*trans* = 40:60), was prepared following the typical procedure M from **162** (24.03 mg, 0.104 mmol) and $Pd(OAc)_2$ (20 mol%) to give *cis*-**164** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 4:1); yield: 9.72 mg (37 %). **^{1}H RMN (300 MHz, Chloroform-*d*)** δ (ppm): 8.67 (d, *J* = 4.6 Hz, 1H), 8.20 (d, *J* = 7.9 Hz, 1H), 7.93 (td, *J* = 7.8, 1.6 Hz, 1H), 7.52 (dd, *J* = 7.2, 5.1 Hz, 1H), 4.51 (dd, *J* = 13.0, 6.4 Hz, 1H), 1.74 – 1.66 (m, 1H), 1.61 (d, *J* = 6.5 Hz, 3H), 1.29 (s, 3H), 1.09 (ddd, *J* = 13.3, 8.3, 4.6 Hz, 2H). **^{13}C-RMN (75 MHz, Chloroform-*d*)** δ (ppm): 173.5, 150.0, 138.1, 127.6, 124.6, 124.3, 61.3, 27.1, 24.3,

20.4, 20.3, 16.0. **HRMS-FAB** calcd. for $C_{12}H_{15}N_2O_3S$ $(M+H)^+$: 267.0803; Found: 267.0800. **IR** (v_{max}/cm^{-1}): 1743 (C=O).

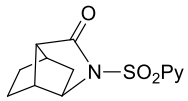
***trans*-4,5-Dimethyl-3-(pyridin-2-ylsulfonyl)-3-azabicyclo[3.1.0]hexan-2-one**



(*trans*-164). Compound *trans*-**164**, obtained together with *cis*-**164**, (*cis*/*trans* = 40:60), was prepared following the typical procedure M from **162** (24.03 mg, 0.104 mmol) and $Pd(OAc)_2$ (20 mol%) to give *trans*-**164** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 4:1); yield: 9.59 mg (36%). **^{1}H RMN (300 MHz, Chloroform-*d*)** δ (ppm): 8.68 (d, *J* = 4.7 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.93 (t, *J* = 7.8 Hz, 1H), 7.52 (dd, *J* = 7.5, 4.8 Hz, 1H), 4.49 (dd, *J* = 12.3, 6.2 Hz, 1H), 1.70 (dd, *J* = 8.8, 3.0 Hz, 1H), 1.64 (d, *J* = 6.2 Hz, 3H), 1.34 (s, 3H), 1.14 – 1.09 (m, 1H), 0.99 (dd, *J* = 8.9, 5.1 Hz, 1H). **^{13}C RMN (75 MHz, Chloroform-*d*)** δ (ppm): 175.2, 150.1, 138.1, 137.9, 127.4, 124.3, 62.6, 28.9, 26.7, 18.3, 18.2, 16.8. **HRMS-FAB** calcd. for $C_{12}H_{15}N_2O_3S$ $(M+H)^+$: 267.0803; Found: 267.0799. **IR** (v_{max}/cm^{-1}): 1741 (C=O).

- ***Carbonylation of "normal" methylene C(sp^3)–H bonds***

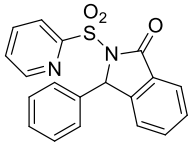
2-(Pyridin-2-ylsulfonyl)hexahydro-1,4-methanocyclopenta[*c*]pyrrol-3(2*H*)-one



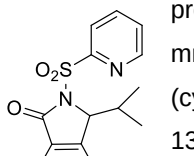
(167). Compound **167**, was prepared following the typical procedure M from **165** (25.20 mg, 0.104 mmol) and $Pd(OAc)_2$ (20 mol%) to give **167** as a brown oil after flash column chromatography (cyclohexane/EtOAc 4:1); yield: 13.9 mg (50%). **^{1}H RMN (300 MHz, Chloroform-*d*)** δ (ppm): 8.92 (s, 1H), 8.09 (t, *J* = 7.7 Hz, 1H), 7.93 – 7.76 (m, 1H), 7.57 – 7.48 (m, 1H), 2.75 (s, 1H), 2.17 (s, 1H), 1.56 (s, 3H), 1.42 (s, 2H), 1.36 – 1.26 (m, 3H). **^{13}C RMN (75 MHz, Chloroform-*d*)** δ (ppm): 173.2, 156.0, 150.0, 138.1, 127.6, 124.6, 58.6, 23.4, 20.4, 19.8, 12.3. **HRMS-ESI** calcd. for $C_{13}H_{15}N_2O_3S$ $(M+H)^+$: 279.0797; Found: 279.0802. **IR** (v_{max}/cm^{-1}): 1739, 1513, 1471.

- ***C(sp^2)–H versus C(sp^3)–H carbonylation***

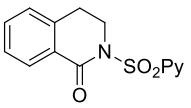
3-Phenyl-2-(pyridin-2-ylsulfonyl)isoindolin-1-one (170). Compound **170** was prepared following the typical procedure M from **168** (33.74 mg, 0.104 mmol) to give **170** as a yellow oil after flash column chromatography (cyclohexane/EtOAc 3:1 to 1:2); yield: 14.58 mg (40%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.57 (dt, *J* = 4.7, 1.2 Hz, 1H), 8.13 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.88 (td, *J* = 7.8, 1.7 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.58 (td, *J* = 7.5, 1.2 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.32 (s, 5H), 7.24 - 7.16 (m, 1H). **HRMS-ESI** calcd. for $C_{10}H_{13}N_2O_3S$ $(M+H)^+$: 241.0641; Found: 241.0641. **IR** (ν_{max}/cm^{-1}) 1734, 1583, 1455, 1438.



3-Isopropyl-2-(pyridin-2-ylsulfonyl)isoindolin-1-one (171). Compound **171** was prepared following the typical procedure M from **169** (30.20 mg, 0.104 mmol) to give **171** as a white solid after flash column chromatography (cyclohexane/EtOAc 4:1 to 2:1); yield: 30.27 mg (92%); mp = 135–137 ºC. **^{1}H NMR (300 MHz, Acetone-d_6)** δ (ppm): 8.62 (d, *J* = 4.7 Hz, 1H), 8.34 - 8.22 (m, 1H), 8.18 (td, *J* = 7.7, 1.6 Hz, 1H), 7.85 - 7.63 (m, 4H), 7.58 (t, *J* = 7.3 Hz, 1H), 5.48 (d, *J* = 3.2 Hz, 1H), 3.04 (dtt, *J* = 10.2, 7.0, 3.1 Hz, 1H), 1.29 (d, *J* = 7.1 Hz, 3H), 0.52 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Acetone-d_6)** δ (ppm): 167.5, 157.2, 151.0, 145.5, 139.3, 134.7, 130.9, 129.8, 128.9, 125.3, 125.2, 124.9, 68.9, 32.6, 19.3, 15.4. **HRMS-ESI** calcd. for $C_{16}H_{17}N_2O_3S$ $(M+H)^+$: 317.0954; Found: 317.0948. **IR** (ν_{max}/cm^{-1}) 1724, 1579, 1466, 1424, 1363.



2-(Pyridin-2-ylsulfonyl)-3,4-dihydroisoquinolin-1(2*H*)-one (173). Compound **173** was prepared following the typical procedure M from **172** (26.20 mg, 0.104 mmol) to give **173** as a white after flash column chromatography (cyclohexane/EtOAc 3:1); yield: 28.20 mg (98%); mp = 169-171 ºC. **^{1}H RMN (300 MHz, Chloroform-*d*)** δ (ppm): 8.62 (d, *J* = 4.4 Hz, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 7.98 (td, *J* = 7.9, 1.6 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.43 (m, 2H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.27 (dd, *J* = 8.0, 4.3 Hz, 1H), 4.40 (t,



J = 6.3 Hz, 2H), 3.21 (t, *J* = 6.2 Hz, 2H). **^{13}C-RMN (75 MHz, Chloroform-*d*)** δ (ppm): 164.1, 157.0, 150.0, 139.9, 138.0, 133.9, 129.3, 128.0, 127.7, 127.6, 127.4, 124.5, 46.1, 29.0. **HRMS-ESI** calcd. for $C_{14}H_{13}N_2O_3S$ $(M+H)^+$: 289.0647; Found: 289.0634. **IR** (ν_{max}/cm^{-1}) 1678, 1603, 1579.

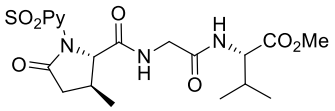
- ***Carbonylation of di- and tripeptides***

(*S*)-Methyl-2-[3,3-dimethyl-5-oxo-1-(pyridin-2-ylsulfonyl]pyrrolidine-2-carboxamido)acetate (177). Compound **177** was prepared following the typical procedure M from **175** (35.71 mg, 0.104 mmol) to give **177** as a white solid after flash column chromatography (cyclohexane/EtOAc 2:1 to 1:2); yield: 33.42 mg (87%); mp = 89-91 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.68 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.24 (dt, *J* = 7.9, 1.1 Hz, 1H), 8.00 (td, *J* = 7.8, 1.7 Hz, 1H), 7.86 (t, *J* = 5.5 Hz, 1H), 7.58 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 4.49 (s, 1H), 4.24 (dd, *J* = 18.2, 5.5 Hz, 1H), 4.05 (dd, *J* = 18.2, 5.1 Hz, 1H), 3.76 (s, 3H), 2.72 (d, *J* = 16.8 Hz, 1H), 2.13 (d, *J* = 16.8 Hz, 1H), 1.30 (s, 3H), 1.22 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 173.3, 170.1, 168.7, 155.5, 150.0, 138.8, 128.1, 124.4, 70.6, 52.5, 45.3, 41.5, 37.9, 29.3, 23.7. **HRMS-ESI** calcd. for $C_{15}H_{20}N_3O_6S$ $(M+H)^+$: 370.1067; Found: 370.1072. **$[\alpha]_D^{25}$**: -11 (*c* = 0.25; Acetone). **IR** (ν_{max}/cm^{-1}) 1756, 1685, 1657,1561, 1435, 1356.

Methyl-2-[(2*S*,3*S*)-3-methyl-5-oxo-1-(pyridin-2-ylsulfonyl]pyrrolidine-2-carboxamido)acetate (178). Compound **178** was prepared following the typical procedure M from **176** (34.25 mg, 0.104 mmol) to give **178** as a white solid after flash column chromatography (cyclohexane/EtOAc 2:1 to 1:2); yield: 28.46 mg (77 %), *cis*/*trans* = 13:87; mp = 213-215 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.86 (s, 1H), 8.77 – 8.60 (m, 1H), 8.24 (dt, *J* = 7.9, 1.1 Hz, 1H), 8.03 (td, *J* = 7.8, 1.7 Hz, 1H), 7.61 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 4.57 (d, *J* = 1.7 Hz, 1H), 4.35 (dd, *J* = 18.1, 6.3 Hz, 1H), 3.98 (dd, *J* = 18.1, 4.5 Hz, 1H), 3.76 (s, 3H), 2.98 – 2.76 (m, 2H), 2.19 – 1.93 (m, 1H), 1.31 (d,

J = 6.4 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 173.9, 170.2, 170.1, 155.5, 150.0, 139.0, 128.2, 124.4, 67.4, 52.4, 41.7, 38.7, 33.3, 20.5. **HRMS-ESI** calcd. for $C_{14}H_{18}N_3O_6S$ $(M+H)^+$: 356.0910; Found: 356.0908. **$[\alpha]_D^{25}$**: -31 (*c* = 0.25; Acetone). **IR** (ν_{max}/cm^{-1}) 1748, 1722, 1687, 1578, 1534, 1427.

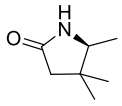
(*S*)-Methyl-3-methyl-2-{2-[(2S,3S)-3-methyl-5-oxo-1-(pyridin-2-ylsulfonyl)pyrrolidine-2-carboxamido]acetamido}butanoate (181). Compound



181 was prepared following the typical procedure M from **180** (42.90 mg, 0.104 mmol) to give **181** as a white solid after flash column chromatography (cyclohexane/EtOAc 3:1); yield: 22.26 mg (71%), *trans*-diastereoselective; mp = 199-201 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 9.27 (s, 1H), 8.72 (d, *J* = 4.4 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 8.06 (t, *J* = 7.8 Hz, 1H), 7.63 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 4.61 (s, 1H), 4.48 (dd, *J* = 8.7, 5.1 Hz, 1H), 4.12 (ddd, *J* = 35.3, 16.2, 5.8 Hz, 2H), 3.70 (s, 3H), 2.84 (dd, *J* = 18.6, 5.7 Hz, 2H), 2.11 (dt, *J* = 19.2, 8.0 Hz, 2H), 1.34 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H). **^{13}C-RMN (75 MHz, Chloroform-*d*)** δ (ppm): 173.9, 172.1, 170.7, 169.1, 155.4, 150.1, 139.2, 128.4, 124.6, 67.3, 57.5, 52.3, 44.0, 38.6, 33.2, 31.1, 20.7, 19.0, 17.8. **HRMS-ESI** calcd. for $C_{19}H_{27}N_4O_7S$ $(M+H)^+$: 455.1594; Found: 455.1594. **$[\alpha]_D^{25}$**: +11 (*c* = 0.15; CH_2Cl_2). **IR** (ν_{max}/cm^{-1}): 1744, 1670, 1656, 1532, 1361.

4.3.6. Deprotection of *N*-(2-pyridyl)sulfonyl group

(*S*)-4,4,5-Trimethylpyrrolidin-2-one (150). To a solution of **149** (60.00 mg, 0.22

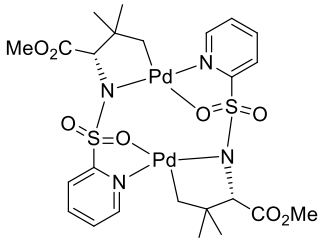


mmol) in MeOH (10 mL) were added Mg turnings (163.0 mg, 6.71 mmol). The reaction mixture was then stirred under sonication at rt overnight. After that time, the reaction mixture was filtered through a pad of Celite although the Mg was completely dissolved. The filtrate was then concentrated and it was dissolved in AcOEt (20 mL). After successively washes with 1 M HCl (1 x 10 mL) and a saturated aq. solution of $NaHCO_3$ (1 x 10 mL), the organic phase was concentrated to dryness. Compound **150** was obtained without any further

purification as a yellowish solid; 25.2 mg (90%); mp = 79-81 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 6.18 (s, 1H), 3.39 (qd, *J* = 6.6, 0.7 Hz, 1H), 2.14 (d, *J* = 3.6 Hz, 2H), 1.12 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.99 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 177.3, 59.2, 46.0, 38.6, 27.1, 22.5, 15.6. **HRMS-GC-EI** calcd. for $C_7H_{13}NO$ $(M)^+$: 127.0997; Found: 127.1001. **$[\alpha]_D^{25}$**: -19 (*c* =0.5; CH_2Cl_2). **IR** (ν_{max}/cm^{-1}) 1694, 1668, 1651, 1425, 1312.

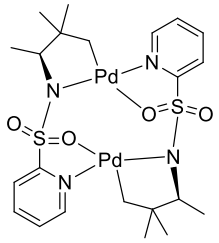
4.3.7. Preparation of palladium complexes

- ***Preparation of bimetallic complex $C_{24}H_{32}N_4O_8Pd_2S_2$ (Complex A).*** An



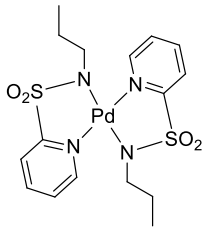
oven dried Ace Pressure tube with Teflon stir bar was charged with **130** (401 mg, 1.40 mmol), $Pd(OAc)_2$ (314 mg, 1.40 mmol) and anhydrous acetonitrile (1.40 mL). The pressure tube was then sealed with a screw-cap and the reaction was placed in a preheated oil bath at 60 ºC and stirred for 2 h. At this point, the reaction mixture was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was then diluted with CH_2Cl_2, filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by crystallisation (hexane/CH_2Cl_2) to afford the bimetallic **complex A** as a yellow solid, yield: 884 mg (91%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.25 (d, *J* = 5.1 Hz, 2H), 7.98 (dt, *J* = 7.6, 3.8 Hz, 2H), 7.90 (d, *J* = 6.7 Hz, 2H), 7.49 (ddd, *J* = 7.2, 5.5, 1.5 Hz, 2H), 3.81 (s, 6H), 3.28 (s, 2H), 3.19 (d, *J* = 6.6 Hz, 2H), 2.15 (d, *J* = 6.2 Hz, 2H), 0.90 (s, 6H), 0.84 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 172.6, 158.2, 149.1, 138.8, 127.3, 125.4, 73.1, 51.8, 47.7, 45.4, 29.3, 23.1. **$[\alpha]_D^{25}$**: +102 (*c* = 0.5; CH_2Cl_2). **IR** (ν_{max}/cm^{-1}) 1743, 1628, 1592, 1449, 1424, 1269. **HRMS-ESI in CH_2Cl_2** (the dimereric species is the predominant) calcd. for $C_{24}H_{32}N_4O_8Pd_2S_2$ $(M+H)^+$: 780.9818; Found: 780.9782. **HRMS-ESI in MeCN** (the monomeric species are the predominants) calcd. for $C_{14}H_{20}N_3O_4PdS$ $(M+H)^+$: 432.0209; Found: 432.0198; calcd. for $C_{12}H_{17}N_2O_4PdS$ $(M+H)^+$: 390.9943; Found: 390.9872.

- ***Preparation of bimetallic complex $C_{22}H_{32}N_4O_4Pd_2S_2$ (Complex C).*** An



oven dried Ace Pressure tube with Teflon stir bar was charged with **148** (48.46 mg, 0.20 mmol), $Pd(OAc)_2$ (44.90 mg, 0.20 mmol) and anhydrous acetonitrile (0.20 mL). The pressure tube was then sealed with a screw-cap and the reaction was placed in a preheated oil bath at 60 ºC and stirred for 3.5 hours. At this point, the reaction mixture was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was then diluted with CH_2Cl_2, filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by crystallisation (hexane/CH_2Cl_2) to afford the bimetallic **complex C** as a yellow solid, yield: 126.29 mg (91%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.19 (d, *J* = 5.2 Hz, 2H), 7.92 (m, 4H), 7.39 (ddd, *J* = 7.2, 5.5, 1.9 Hz, 2H), 3.00 (d, *J* = 6.7 Hz, 2H), 2.85 (q, *J* = 6.3 Hz, 2H), 2.14 (d, *J* = 6.7 Hz, 2H), 1.36 (d, *J* = 6.4 Hz, 6H), 0.80 (s, 6H), 0.68 (s, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 159.9, 148.2, 138.3, 126.2, 125.1, 67.2, 46.6, 44.8, 30.0, 23.1, 19.5. **HRMS-ESI** calcd. for $C_{22}H_{33}N_4O_4Pd_2S_2$ $(M+H)^+$: 693.0004; Found: 692.9988. **$[\alpha]_D^{25}$**: -21 (*c* = 0.17; Acetone). **IR** (ν_{max}/cm^{-1}) 1591, 1548, 1434, 1376, 1276, 1124.

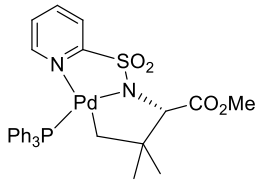
- ***Preparation of the monomeric complex $C_{16}H_{22}N_4O_4S_2Pd$ (Complex D).*** An



oven dried Ace Pressure tube with Teflon stir bar was charged with **154** (41.66 mg, 0.20 mmol), $Pd(OAc)_2$ (22.45 mg, 0.10 mmol) and 1,1,1,3,3,3-hexafluoro-2-propanol (0.1 mL). The pressure tube was then sealed with a screw-cap and the reaction was placed in a preheated oil bath at 60 ºC and stirred for 3 h. At this point, the reaction mixture was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was then diluted with CH_2Cl_2, filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by crystallisation (hexane/CH_2Cl_2) to afford the bimetallic **complex D** as a yellow solid, yield: 42.92 mg (85%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.87 (d, *J* = 5.3 Hz, 2H), 8.12 (td, *J* = 7.8, 1.4 Hz, 2H), 7.87

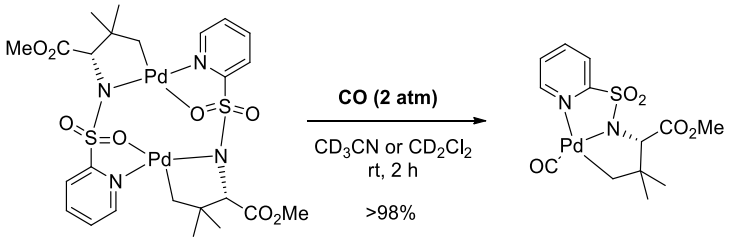
(d, *J* = 7.7 Hz, 2H), 7.63 – 7.43 (m, 2H), 3.00 – 2.47 (m, 4H), 1.89 – 1.42 (m, 4H), 0.76 (t, *J* = 7.3 Hz, 6H). **HRMS-ESI** calcd. for $C_{16}H_{22}N_4O_4S_2PdNa$ $(M+Na)^+$: 527.0196; Found: 527.0037.

- ***Preparation of the monomeric complex $C_{30}H_{31}N_4O_4PSPd$ (Complex E).***



To a solution of bimetallic **complex A** (10.00 mg, 0.013 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (0.1 mL), PPh_3 (6.60 mg, 0.025 mmol, 1.0 equiv respect to the Pd) was added and the mixture was stirred at room temperature for 18 h. At this point, the reaction mixture was concentrated under reduced pressure. The solid was purified by trituration (CH_2Cl_2/hexane) to afford the monomeric complex **complex E** as a white solid; yield: 15.09 mg (92%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.02 (d, *J* = 7.9 Hz, 1H), 7.90 – 7.77 (m, 1H), 7.76 – 7.58 (m, 6H), 7.54 – 7.34 (m, 9H), 7.01 – 6.83 (m, 2H), 4.19 (s, 1H), 3.74 (s, 3H), 1.83 (dd, *J* = 9.5, 3.8 Hz, 1H), 1.74 (dd, *J* = 9.4, 6.2 Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 173.5 (d, *J* = 1.3 Hz), 163.2, 148.6, 139.4, 134.5 (d, *J* = 12.7 Hz), 131.3, 131.1 (d, *J* = 2.2 Hz), 130.7, 128.9 (d, *J* = 10.4 Hz), 126.1, 122.7, 64.6, 53.0, 51.6, 47.3, 29.7, 25.8. **^{31}P NMR (122 MHz, Chloroform-*d*)** δ 35.1. **HRMS-ESI** calcd. for $C_{30}H_{32}N_2O_4PPdS$ $(M+H)^+$: 653.0861; Found: 653.0835.

4.3.8. Characterization of Intermediate B in CD_3CN and CD_2Cl_2



Complex A **Intermediate B**

A solution of **complex A** (30.0 mg, 0.038 mmol) in 1.0 mL of CD_3CN or CD_2Cl_2, was heated at room temperature under a 2 atm of CO. After that time, **intermediate B** was quantitatively formed and inmediatly characterized due to its instability.

- **Characterization of intermediate B in CD_3CN: ^{1}H NMR (500 MHz, Acetonitrile-*d*)** δ (ppm): 8.49 (d, *J* = 4.6 Hz, 1H), 8.21 (td, *J* = 7.9, 1.6 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.70 (ddd, *J* = 7.7, 5.2, 1.3 Hz, 1H), 3.86 (s, 1H), 3.67 (s, 3H), 2.82 (d, *J* = 9.2 Hz, 1H), 2.40 (d, *J* = 9.1 Hz, 1H), 1.38 (s, 3H), 1.05 (s, 3H). **^{13}C NMR (125 MHz, Acetonitrile-*d*)** δ (ppm): 179.0, 173.4, 161.3, 152.4, 142.7, 129.1, 125.4, 122.6, 65.1, 53.6, 52.0, 43.4, 30.2, 25.2. **HRMS-ESI** calcd. for $C_{13}H_{16}N_2NaO_5PdS$ $(M+CO+Na)^+$: 440.9712; Found: 440.9716. Calcd. for $C_{12}H_{16}N_2NaO_4PdS$ $(M-CO+Na)^+$: 412.9762; Found: 412.9700. Calcd. for $C_{26}H_{32}N_4NaO_{10}Pd_2S_2$ $(2M+2CO+Na)^+$: 860.9539; Found: 860.9541. **IR** (ν_{max}/cm^{-1}) 2095, 1742, 1592.

- **Characterization of intermediate B in CD_2Cl_2: ^{1}H NMR (300 MHz, Dichloromethane-*d*)** δ (ppm): 8.34 (d, *J* = 5.2 Hz, 1H), 8.12 (td, *J* = 7.9, 1.4 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.68 – 7.39 (m, 1H), 3.93 (s, 1H), 3.70 (s, 3H), 2.87 (d, *J* = 9.1 Hz, 1H), 2.43 (d, *J* = 9.1 Hz, 1H), 1.40 (s, 3H), 1.07 (s, 3H). **^{13}C NMR (75 MHz, Dichloromethane-*d*)** δ (ppm): 179.2, 173.3, 162.2, 150.9, 141.7, 128.3, 123.1, 65.3, 52.0, 44.6, 30.7, 27.5, 25.5. **HRMS-ESI** calcd. for $C_{13}H_{17}N_2O_5PdS$

$(M+CO+H)^+$: 418.9893; Found: 418.9881. Calcd. for $C_{12}H_{17}N_2O_4PdS$ $(M-CO+H)^+$: 390.9943; Found: 390.9885. **IR** (ν_{max}/cm^{-1}) 2096, 1743, 1595.

4.3.9. DOSY NMR experiments

The spectra were recorded on a Bruker DRX 500 spectrometer, using a BBOF Bruker 5-mm probe with Z-gradients. The temperature was regulated at (278 K) and (298 K) and no spinning was applied to the NMR tube. The diffusion NMR experiments were performed with a pulse-field gradient stimulated echo (PFGSTE) sequence, using bipolar gradients (ledbpgp2s).[261,262] The bipolar gradient duration and the diffusion time were optimized to 1.4 and 50 ms, respectively. DOSY spectra were generated by using the DOSY processing module in TopSpin v3.2 software. Diffusion coefficients *D* were derived fitting the intensity or the area of the desired peaks to a single exponential decay, using the Bruker software package T1/T2 Relaxation in the same program. The value of the diffusion coefficient *D* in a mixture of **complex A**: **intermediate B**, was determined from and average of all the analyzed peaks (the final value for each peak is the average of 9-14 measured values). Molecular weights were calculated from measured diffusion coefficients applying the model proposed by Evans and the Excel spreadsheet provided by the authors.[235] The corresponding hydrodynamic radius was estimated by the Stokes-Einstein equation.[236]

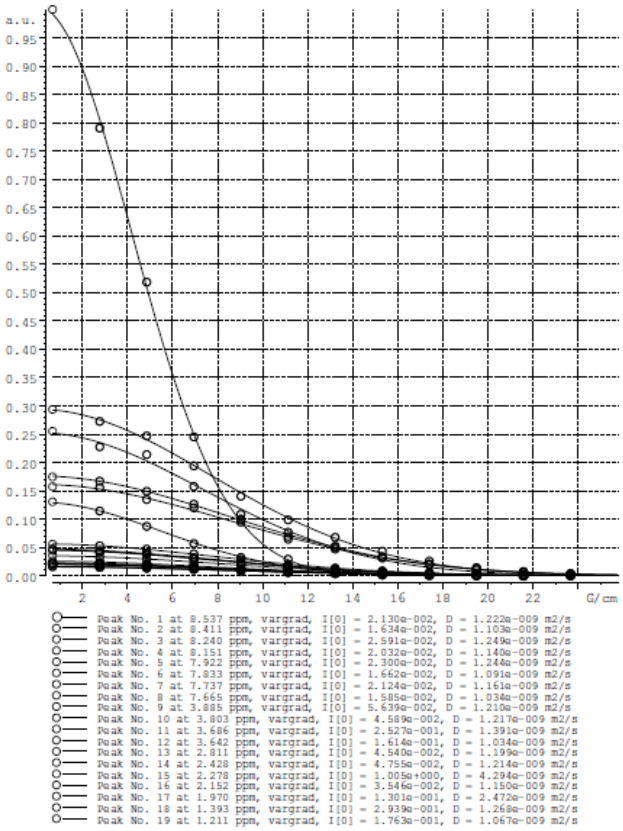
[261] J. E. Tanner, *J. Chem. Phys.* **1970**, *52*, 2523.

[262] a) R. Johnson, *Prog. Nucl. Magn. Reson. Spectrosc.* **1999**, *34*, 203. b) R. M. Cotts, M. J. R. Hoch, T. Sun, J. T. Marker, *J. Magn. Reson.* **1989**, 252.

- **DOSY NMR experiment in CD_3CN**

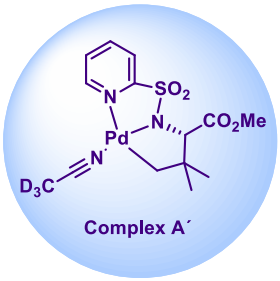
The experiment was carried out at 278 K in CD_3CN. For this experiment, a 58:42 mixture of **complex A´ : intermediate B** was prepared.[263]

a) Graphic representation of the fitted curves to a single exponential decay.



[263] $D = \frac{Kb\,T}{6\pi\,\eta o\,R}$; where D is the diffusion coefficient ($m^2.s^{-1}$); K_b the Boltzmann constant 1.38065 ($J.K^{-1}$); T the temperature (K); η_o the viscosity ($Kg.m^{-1}.s^{-1}$) and R the radius (m). The values employed for CD_3CN at 278 K were found at the online Dortmund Data Bank: density ρ = 0.7978 $g.mL^{-1}$; viscosity η_o = 0,419 x 10^{-3} $Kg.m^{-1}.s^{-1}$; MW = 44,0704 $g.mol^{-1}$.

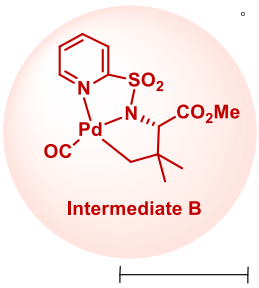
D = 1.092E-09 m^2/sg



R = 4.45 Å

MW = 434.82 g/mol
MW_c = 443.20 g/mol
MW/MW_c ratio = 0.98

D = 1.214E-09 m^2/sg



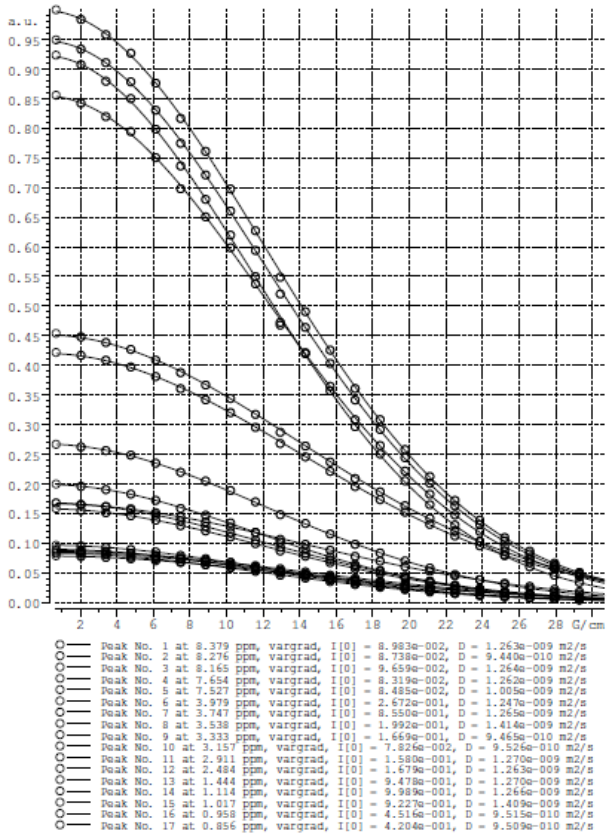
R = 4.00 Å

MW = 419.77 g/mol
MW_c = 350.80 g/mol
MW/MW_c ratio = 1.19

- **DOSY NMR experiment in CD_2Cl_2**

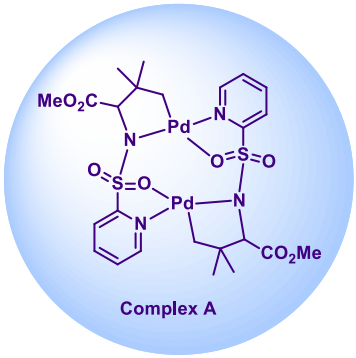
The experiment was carried out at 298 K in CD_2Cl_2. For this experiment, a 40:60 mixture of **complex A:intermediate B** was prepared.[264]

a) Graphic representation of the fitted curves to a single exponential decay.



[264] $D = \frac{Kb\,T}{6\pi\,\eta o\,R}$; where D is the diffusion coefficient ($m^2.s^{-1}$); K_b the Boltzmann constant 1.38065 ($J.K^{-1}$); T the temperature (K); η_o the viscosity ($Kg.m^{-1}.s^{-1}$) and R the radius (m). The values employed for CD_2Cl_2 at 298 K were found at the online Dortmund Data Bank: density ρ = 1.3620 $g.mL^{-1}$; viscosity η_o = 0,420 x 10^{-3} $Kg.m^{-1}.s^{-1}$; MW = 86.9403 $g.mol^{-1}$.

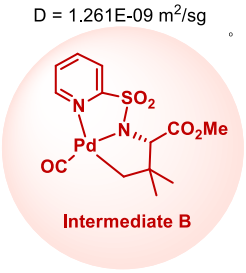
D = 9.491E-10 m^2/sg



R = 5.52 Å

MW = 781.50 g/mol
MW_c = 682.90 g/mol
MW/MW_c ratio = 1.14

D = 1.261E-09 m^2/sg



R = 4.11 Å

MW = 419.77 g/mol
MW_c = 372,80 g/mol
MW/MW_c ratio = 1.12

ANNEX I

Asymmetric Direct Mannich Reaction of Glycine Schiff Bases with aliphatic α-Amido Sulfones

Annex I. Asymmetric Direct Mannich Reaction of Glycine Schiff Bases with aliphatic α-Amido Sulfones

A.1. Importance of α,β-diamino acid derivatives and asymmetric catalysis synthesis

The importance of chirality is not just reflected in its enormous influence in the development of the vast majority of biological systems vital functions but also in the increasing and continuous demand of enantiomerically enriched products.[265] As a result, chiral compound asymmetric synthesis constitutes a very relevant area in modern chemistry. Due to its intrinsic characteristic of both atom and step economy, asymmetric catalysis, where a prochiral substrate is converted into a chiral product under a substoichiometric amount of a chiral catalyst, provides the conceptually more efficient alternative for the preparation of enantiomerically enriched compounds.[266,267]

In this context, the enantioselective catalytic synthesis of α,β-diamino acid derivatives, which has become a stimulating and active area of research, represents

[265] For selected reviews on chiral compounds applications, see: a) P. Ravarello, *Furure Med. Chem.* **2009**, *1*, 35. b) E. Francotte, W. Lindner, *Chirality on Drug Discovery*, Wiley-VCH, **2006**. c) M. Nogradi, *Stereoselective Synthesis*, Wiley-VCH, Weinheim, **1995**.

[266] For selected textbooks on asymmetric catalysis, see: a) P. J. Walsh, M. C. Kzlowski, *Fundamentals of Asymmetric Catalysis*, University Science Books, USA, **2009**. b) M. Christmann, S. Bräse, *Asymmetric Catalysis: The Essentials*, Wiley-VCH, New York **2007**. c) K. Mikami, M. Lautens, *New Frontiers in Asymmetric Catalysis*, Wiley-VCH, Weinheim, **2007**. d) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis*, Springer, Heidelberg, **2004**.

[267] Chiral organometallic catalysts constitute the most common source of asymmetric induction. However, during the last years, organocatalysis has been developed as a greener alternative for this purpouse. For selected reviews on organometallic asymmetric catalysis, see: a) J. –A. Ma, D. Cahard, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. b) S. V. Malhotran, *Methodologies in Asymmetric Catalysis*, Oxford University Press, New York, **2004**. For selected reviews on asymmetric organocatalysis, see: c) B List, *Asymmetric Organocatalysis*, Springer, Heidelberg, **2010**. d) A. Berkessel, H. Gröger, *Metal-free Organic Catalysts in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2004**. See also: e) C. Gromndal, J. Mattiew, D. Enders, *Nature Chem.* **2010**, *2*, 167. f) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.

a challenging approach due to the necessity of controlling two contiguous stereocenters.[268]

This structural motif is shared by many bioactive natural products and therapeutic agents, including peptide and β-lactam antibiotics. In addition, owing to its polyfunctional nature, optically active α,β-diamino acid derivatives serve as versatile building blocks for the synthesis of new molecules or as potential surrogates in known peptide entities to modulate their conformational, physicochemical and biological properties.[269] As a consequence, increasing interest is being devoted to the development of highly efficient and general methods for the asymmetric construction of this structurally simple, yet polyfunctional structure.

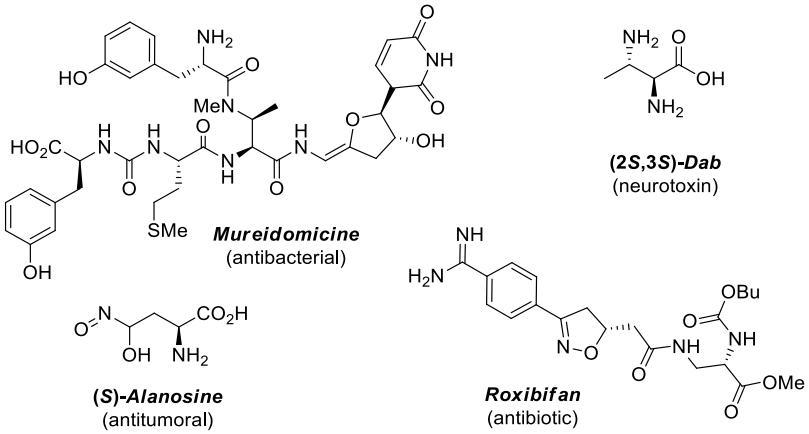
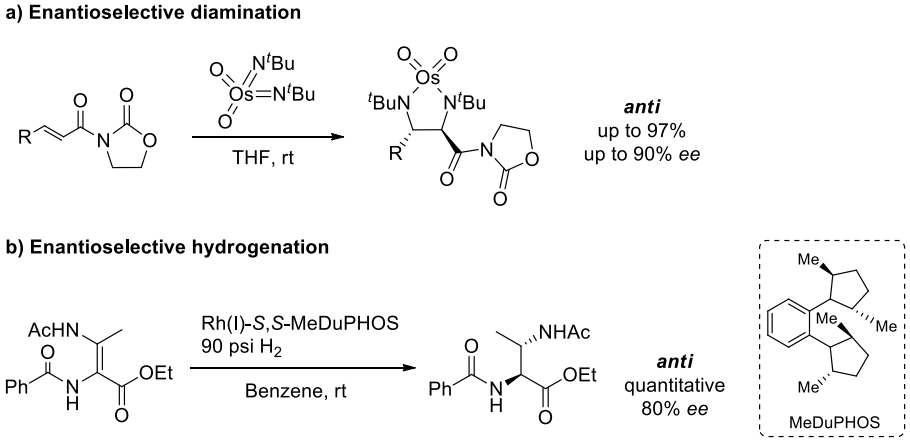


Figure A.1

[268] For selected reviews on the synthesis and biological importance of α,β-diamino acid derivatives, see: a) A. Viso, R. Fernández de la Pradilla, M. Tortosa, A. García, A. Flores, *Chem. Rev.* **2011**, *111*, PR1-PR42. b) A. Viso, R. Fernández de la Pradilla, A. García, A. Flores, *Chem. Rev.* **2005**, *105*, 3167.

[269] For a review on the structural chemistry of peptides, see: P. G. Vasudev, S. Chatterjee, N. Shamala, P. Balaram, *Chem. Rev.* **2011**, *111*, 657.

For this purpose, different catalytic asymmetric approaches are reported in the literature. Diamination (Scheme A.1a)[270] and catalytic hydrogenation (Scheme A.1b)[271] have efficiently achieved the synthesis of α,β-diamino acid derivatives, however, while the first method requires stoichiometric amounts of Ti^{IV} or Os^{VIII} species, limiting a large scale synthesis, the second strategy is not useful for synthesizing compounds with tetrasubstituted carbon stereocenters.[272]



Scheme A.1

In sharp contrast, the direct Mannich reaction between a prochiral nitrogen nucleophile and an imine,[273] results in the construction of a C–C bond and two

[270] For selected publications on enantioselective amination, see: a) I. Almodovar, C. H. Hövelmann, J. Streuff, M. Nieger, K. Muñiz, *Eur. J. Org. Chem.* **2006**, 704. b) K. Muñiz, M. Nieger, *Chem. Commun.* **2005**, 2729.

[271] For selected publications on enantioselective hydrogenation, see: a) K. Zeitler, W. Steglich, *J. Org. Chem.* **2004**, *69*, 6134. b) A. J. Robinson, C. Y. Lim, *J. Org. Chem.* **2001**, *66*, 4141. c) A. J. Robinson, P. Stanilawski, D. Mulholland, *J. Org. Chem.* **2001**, *66*, 4148.

[272] For a review on catalytic asymmetric construction of quaternary centers, see: B. M. Trost, C. H. Jiang, *Synthesis* **2006**, 369.

[273] For the use of imines in total synthesis, see: S. F. Martin, *Pure App. Chem.* **2009**, *63*, 571.

neighbouring nitrogen containing stereocenters simultaneously in a single step.[274] This strategy is receiving a tremendous boost through two complementary approaches: a) the direct *aza*-Henry reaction[275] and b) the direct Mannich reaction of glycine ester Schiff bases with imines.

Continuing with this approach, we will next comment the most representative examples of the metal-catalyzed direct Mannich reaction of glycine ester Schiff bases with imines previous to our work.

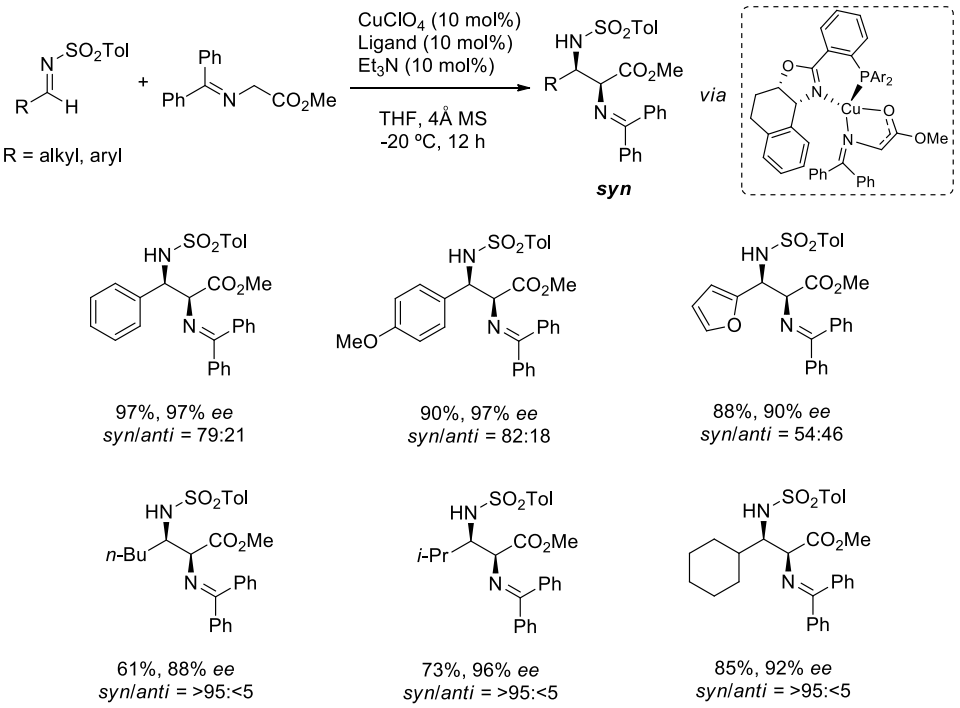
A.1.1. Metal-catalyzed direct Mannich reaction of glycine ester Schiff bases with imines

The first example of a catalytic asymmetric direct Mannich reaction between a glycine ester Schiff base and imines was reported by Jørgensen in 2003, based on a $CuClO_4$/phosphinooxazoline catalyst system (Scheme A.2).[276] While high *syn*-diastereoselectivity (*syn*/*anti* = >95:<5) was observed for aliphatic imines, lower diastereoisomeric ratios (*syn*/*anti* = 61:39 to 86:14) were obtained for aromatic and heteroaromatic aldimines. In both cases, excellent enantiomeric excesses were achieved (88-97% *ee*).

[274] For a recent review on the synthesis of α,β-diamino acid derivatives *via* catalytic asymmetric direct Mannich reaction, see: a) R. Gómez Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940. For reviews on catalytic asymmetric Mannich reactions, see: b) J. M. M. Verkade, L. J. C. vanHemert, M. P. J. L. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29. c) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, *35*, 5797. d) M. M. B. Marques, *Angew. Chem. Int. Ed.* **2006**, *45*, 348. For a review on the application of the Mannich reaction in the total synthesis of natural products, see: e) B. B. Toure, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439.

[275] For selected publications on the *aza*-Henry reaction, see: a) D. Uruguchi, K. Koshimoto, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 10878. b) Z. H. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170. c) A. Singh, R. A. Yoder, B. Shen, J. N. Johnston, *J. Am. Chem. Soc.* **2007**, *129*, 3466. For a review on recent advances in the aza-Henry reaction, see: d) B. Westermann, *Angew. Chem. Int. Ed.* **2003**, *42*, 151.

[276] L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583.

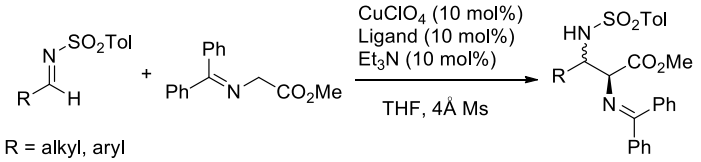


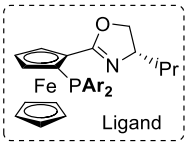
Scheme A.2

Since this pioneering work, other metal-catalyzed approaches have appeared in the literature as efficient strategies for the synthesis of diastereo- and enantio-enriched α,β-diamino acid derivatives. For example in 2008, Wu reported a robust protocol were the *syn*/*anti* configuration was efficiently switched by changing the electronic properties of the chiral ferrocenic Fc-PHOX ligand.[277] While electron-donating *para*-methoxyphenyl rings at the phosphorous atom of the ligand yielded the *anti*-derivatives, electron-withdrawing *para*-fluorophenyl aromatic rings provided the desired *syn*-derivatives. Through this simple modification, either *syn*- or *anti*-α,β-diamino acid derivatives were obtained with high diastereocontrol and excellent

[277] X. –X. Yan, Q. Peng, Q. Li, K. Zhang, J. Yao, X. –L. Hou, Y. –D. Wu, *J. Am. Chem. Soc.* **2008**, *130*, 14362.

enantioselectivities with a variety of aryl and heteroaryl imines as well as an example of the cyclohexyl aliphatic imine.





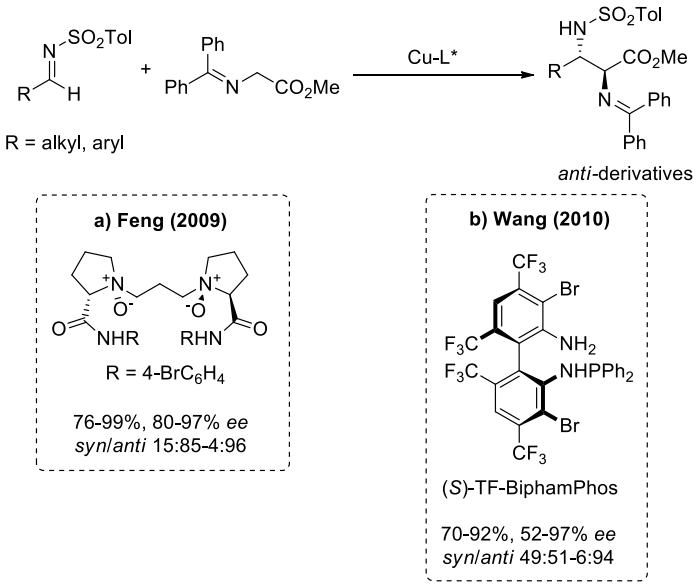
R	Ar = 3,5-$F_2C_6H_3$ *syn*/*anti*	Ar = 3,5-$F_2C_6H_3$ *ee* (%)	Ar = 4-$OMeC_6H_4$ *syn*/*anti*	Ar = 4-$OMeC_6H_4$ *ee* (%)
Ph	4:96	99	>95:<5	99
3-$OMeC_6H_4$	6:94	96	93:7	99
4-BrC_6H_4	9:91	99	95:5	98
2-Furyl	10:90	94	>95:<5	96
Cy	<5:>95	97	>95:<5	99

Scheme A.3

More recently, Feng (Scheme A.4a)[278] and Wang (Scheme A.4b)[279] independently reported highly *anti*-diastereoselective protocols (*syn*/*anti* = 15:85-4:96 and 49:51-6:94, respectively), based on the direct Mannich reaction of methyl glycinate pronucleophile with tosyl aldimines catalyzed by Cu-chiral nitrogenated ligand complexes, achieving in both cases moderate to excellent enantioselectivities (80-97 and 52-97 *ee* %, respectively).

[278] D. Shang, Y. Liu, X. Zhou, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 3678.

[279] G. Liang, M. –C. Tong, H. Tao, C. –J. Wang, *Adv. Synth. Catal.* **2010**, *352*, 1851.



Scheme A.4

A.1.2. Use of α-amido sulfones in asymmetric direct Mannich reaction

In spite of the great advances made in this area of research, most of the glycine direct Mannich reaction reported protocols are restricted to imines derived from aromatic aldehydes,[280] whereas only isolated examples involving more challenging

[280] For other approaches on the synthesis of α,β-diamino acid derivatives *via* asymmetric direct Mannich reaction, see: [Organocatalysis based protocols]; a) S. Nakamura, Y. Maeno, M. Ohara, A. Yamamura, Y. Funahashi, N. Shibata, *Org. Lett.* **2012**, *14*, 2960. b) k) S. Kobayashi, R. Yazaki, K. Seki, Y. Yamashita, *Angew. Chem. Int. Ed.* **2008**, *47*, 5613. [Chiral base/acid catalysis based protocols]; c) S. –H. Shi, F. –P. Huang, P. Zhu, Z. –W. Dong, X. –P. Hui, *Org. Lett.* **2012**, *14*, 2010. d) J. Jiang, H. –D. Xu, J. –B. Xi, B. –Y. Ren, F. –P. Lav, X. Guo, L. –Q. Liang, *J. Am. Chem. Soc.* **2011**, *133*, 8428. e) T. Shibuguchi, H. Mihara, A. Kuramochi, T. Ohshima, M. Shibasaki, *Chem. Asian J.* **2007**, *2*, 794. f) M. M. Salter, J. Kobayashi, Y. Shimizu, S. Kobayashi, *Org. Lett.* **2006**, *8*, 3533. [Phase-transfer catalysis based protocols]; g) A. Okada, T. Shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi, M. Shibasaki, *Angew. Chem. Int. Ed.* **2005**, *44*, 4564. h) T. Ooi, M. Kameda, J. –I. Fujii, K. Maruoka, *Org. Lett.* **2004**, *6*, 2397. For the use of α-isothiocyanates as the nucleophilic

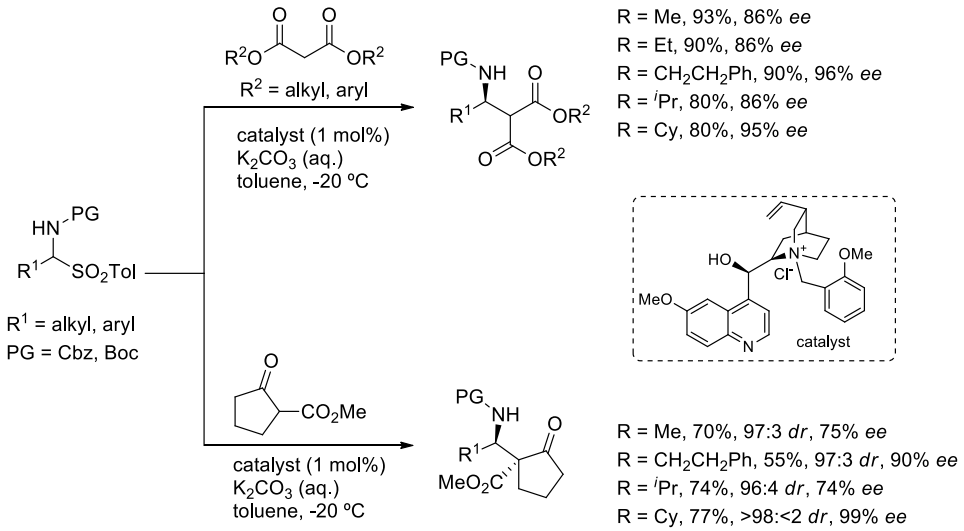
aliphatic imines are described,[281] generally restricted to β-disubstituted imines (cyclohexyl derivative and analogues). A primary reason for this scarcity is the instability of aliphatic imines and their propensity to undergo tautomerization to enamines, thus hampering an efficient nucleophilic addition. An efficient alternative to circumvent these drawbacks is the use of α-amido sulfones which *in situ* generates the corresponding highly reactive aliphatic imine derivative. In fact, during the last decades, significant achievements have been made in the field of catalytic enantioselective reactions involving the use of α-amido sulfones, which are bench-stable compounds, easily prepared, purified and stored for a prolonged time.[282] For example, Ricci reported a highly efficient diastereo- and enantio-selective Mannich reaction of aliphatic α-amido sulfones with malonates and β-keto esters, catalyzed by quiral quaternary ammonium salts (Scheme A.5).[283]

counterpart, see: i) G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2011**, *50*, 4382. j) X. Cheng, S. Dong, Z. Qiao, Y. Zhu, M. Xie, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2011**, *17*, 2583. k) L. Li, M. Gash, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 11648. l) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Köhn, M. C. Willis, *J. Am. Chem. Soc.* **2007**, *129*, 10632.

[281] For the highly enantioselective Mannich reaction of α-substituted azlactones with enolizable aliphatic imines see: a) W. –Q. Zhang, L. –F. Cheng, J. Yu, L. –Z. Gong, *Angew. Chem. Int. Ed.* **2012**, *51*, 4085. b) A. D. Melhado, G. W. Amarante, Z. J. Wang, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 3517.

[282] For a general review on the use of α-amido sulfones, see: a) M. Petrini, *Chem. Rev.* **2005**, *105*, 3949. For a review on the recent application of α-amido sulfones in Mannich reactions, see: b) B. Yin, Y. Zhang, L. –W. Xu, *Synthesis* **2010**, *21*, 3583, and references cited therein.

[283] a) O. Mariannacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, *Chem. Eur. J.* **2007**, *13*, 8338. b) F. Fini, L. Bernardi, R. P. Herrera, D. Pettersen, A. Ricci, V. Sgarzani, *Adv. Synth. Catal.* **2006**, *348*, 2043.



Scheme A.5

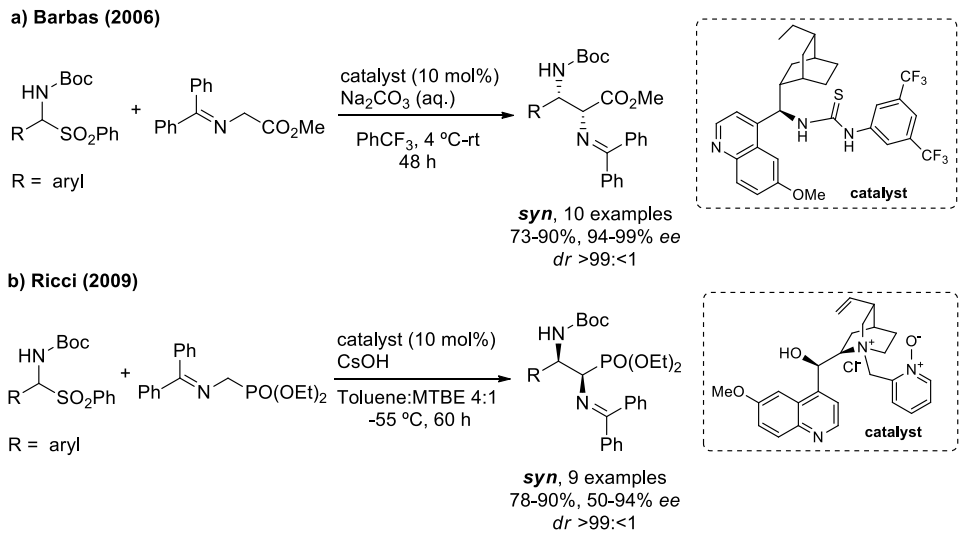
This selected example clearly illustrates the great potential that α-amido sulfones offer to *in situ* generate extremely reactive aliphatic imines. Although this strategy has widely been applied in the asymmetric direct Mannich reaction for the synthesis of α- and/or β-diamino acid derivatives,[282,284] just two protocols were reported when using glycine Schiff bases as pronucleophiles. In 2006, Barbas[285] presented a highly diastero- and enantioselective method for the synthesis of α,β-diamino acid derivatives based on a chincona thiourea catalyst (Scheme A.6a), which was further applied by Ricci,[286] in the synthesis of α,β-diaminophosphonic acid derivatives (Scheme A.6b). However, in both protocols aromatic α-amido sulfones were used,

[284] For selected reviews on the synthesis of α-amino acid derivatives, see: a) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584. b) L. Aurelio, R. T. C. Brownlee, A. B. Hughes, *Chem. Rev.* **2004**, *104*, 5823. For a selected review on recent advances in the catalytic asymmetric synthesis of β-amino acids, see: c) B. Weiner, W. Szymanski, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2010**, *39*, 1656.

[285] H. Zhang, S. Syed, C. F. Barbas, *Org. Lett.* **2010**, *12*, 708.

[286] R. D. Momo, F. Fini, L. Bernardi, A. Ricci, *Adv. Synth. Catal.* **2009**, *351*, 2283.

thus corroborating again that the instability of aliphatic imines makes the use of these substrates very challenging.



Scheme A.6

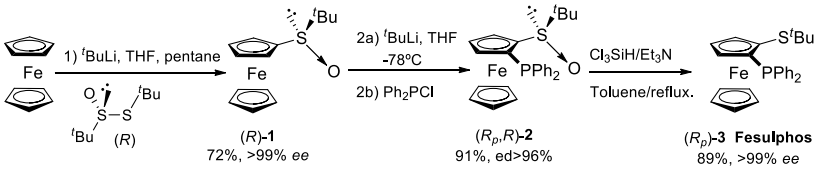
A.1.3. Precedents of our research group based on the asymmetric direct Mannich reaction of glycine Schiff bases with aromatic aldimines

Our research group developed in 2002 the first family of ferrocenic chiral ligands with P,S coordination (1-phosphine-2-sulfenylferrocenes) presenting exclusively planar quirality. These ligands, known as *Fesulphos* derivatives, exhibit different characteristics which make them attractive in asymmetric synthesis: a) formation of a 5-membered metallacycle; b) stable and crystalline, easily purified by crystallization or column chromatography; c) three step synthesis, sulfinilation, *ortho*-phosphinilation and sulfoxide reduction.[287]

[287] a) O. García Mancheño, J. Priego, S. Cabrera, R. Gómez Arrayás, T. Llamas, J. C. Carretero, *J. Org. Chem.* **2003**, *68*, 3679. b) J. Priego, O. García Mancheño, S. Cabrera, R. Gómez Arrayás, T.

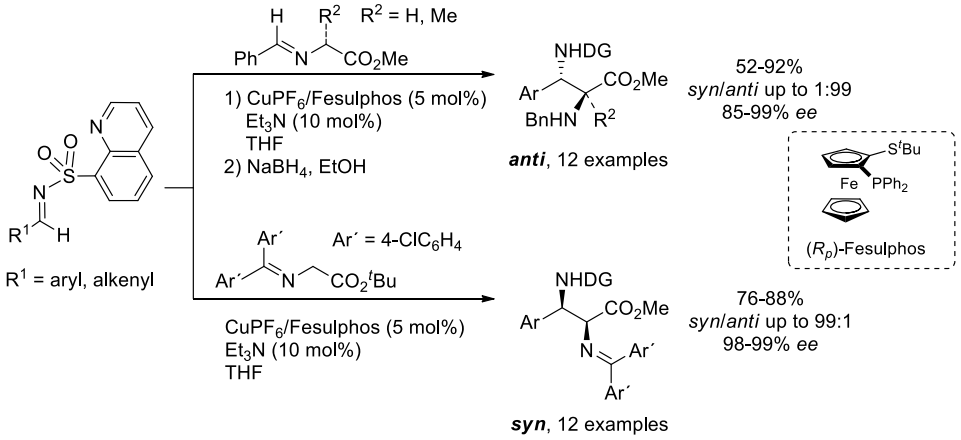
Based on the asymmetric metal-catalyzed precedents, our research group reported an efficient catalytic asymmetric direct Mannich reaction of glycinate derivatives with aromatic aldimines, leading to orthogonally protected α,β-diamino acid derivatives with either *syn*- or *anti*-configuration in a highly diastereo- and enantiocontrolled manner.[288,289] The choice of Fesulphos-Cu^{I} as catalyst was crucial to accomplishing high asymmetric induction (typically ≥ 90% *ee*), while the use of the readily available *N*-(8-quinolyl)sulfonyl-protected aldimines as substrates was a key element determining the high diastereoselectivity. Both the level and the sense of the diastereoselectivity (*syn*- or *anti*-configuration of the products) could be efficiently controlled by tuning the combined steric and electronic properties of the glycinate Schiff base

Llamas, J. C. Carretero, *Chem. Commun.* **2002**, 2512. For the synthesis of the Fesulphos ligand, see Scheme bellow:



[288] a) J. Hernández-Toribio, R. Gómez Arrayás, J. C. Carretero, *Chem. Eur. J.* **2010**, *16*, 1153. b) J. Hernández-Toribio, R. Gómez Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2008**, *130*, 16150.

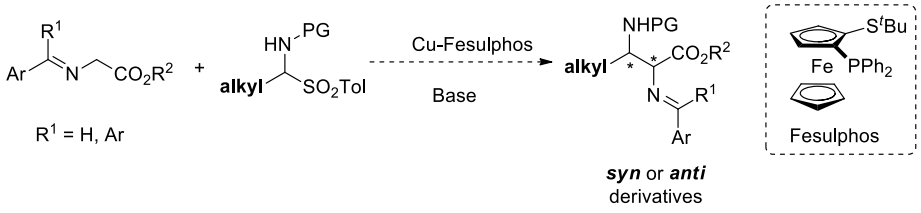
[289] For the use of Fesulphos ligands on indirect Mannich reactions, see: a) A. Salvador González, R. Gómez Arrayás, M. Rodríguez Rivero, J. C. Carretero, *Org. Lett.* **2008**, *10*, 4335. b) A. Salvador González, R. Gómez Arrayás, J. C. Carretero, *Org. Lett.* **2006**, *8*, 2977.



Scheme A.7

A.2 Aim of the project

Based on the excellent results obtained in our Cu^{I}-Fesulphos catalytic asymmetric direct Mannich reaction of glycinate derivatives with aromatic aldimines,[288] we hypothesized that excellent diastereo- and enantio-selectivities could also be achieved for aliphatic imines. We also envisioned that the undesired enamine tautomerization could be avoided by using aliphatic α-amido sulfones as *in situ* precursors of the highly reactive aliphatic imine derivatives,[282] which rapidly would react with the nucleophilic counterpart, yielding the desired β-alkyl-α,β-diamino acid derivatives. Additionally, by a sequential deprotection protocol, differently substituted free α,β-diamino acid derivatives could be obtained.

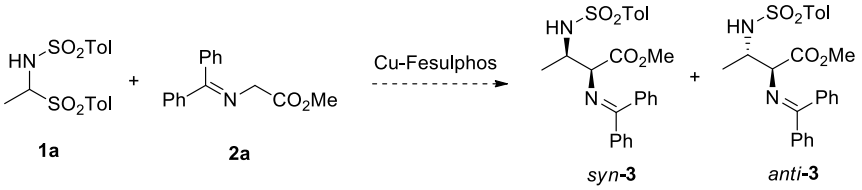


Scheme A.8

A. 3. Results and discussion

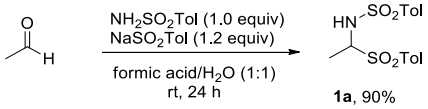
Among, aliphatic imines, those from small linear aldehydes are considered to be very problematic because of the difficulty in controlling their high reactivity. In particular, the imine of acetaldehyde is, to the best of our knowledge, yet to be applied in glycine asymmetric Mannich reaction. Therefore, we chose the model reaction of the α-amido sulfone derived from acetaldehyde **1a**[290] with glycine methyl ester **2a**[291] under Cu^{I}-Fesulphos[292] for reaction parameters optimization.

Model reaction for optimization studies



Scheme A.9

[290] α-Amido sulfones were prepared following a reported protocol from the corresponding aldehyde (1.0 equiv), the corresponding sulfonamide (1.0 equiv) and $TolSO_2Na$ (1.2 equiv) in a 1:1 formic acid/H_2O mixture, at rt for 24 h; see, F. Chemla, V. Hebbe, J. –F. Normandt, *Synthesis*, **2000**, *1*, 75. For the synthesis of **1a**, see Scheme bellow.



[291] Glycine ester derivatives were prepared following reported protocols from the corresponding diarylmethanimine (1.0 equiv), α-amino ester hydrochloride (1.1 equiv) and $MgSO_4$ (1.5 equiv), stirred at rt for 24 h, and used without any further purification, see: a) D. G. Brenner, K. M. Cavolowsky, K. L. Shepard, *J. Het. Chem.* **1985**, *22*, 805. b) M. J. O´Donnell, R. L. Polt, *J. Org. Chem.* **1982**, *47*, 2663.

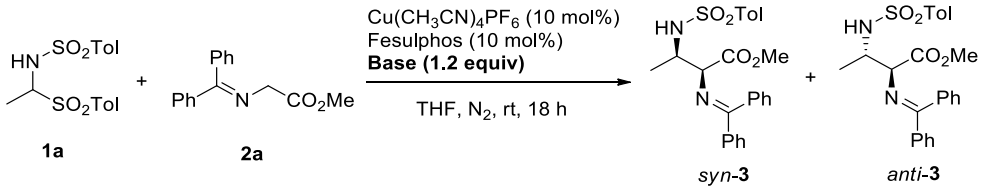
[292] Fesulphos ligand was prepared following the procedure reported by our group, see reference 287. This ligand is also commercially available, CAS number: 503859-61-8.

A.3.1. Optimization studies

- ***Study of the base***

We started our optimization studies by testing a wide range of organic and inorganic bases, which would be crucial for the *in* situ formation of the corresponding reactive imine (Table A.1). While Et_3N, previously reported in our group for the glycine Mannich reaction with aromatic imines, completely inhibited the reaction (entry 1), other nitrogenated bases, such as diisopropylamine or diisopropylethylamine resulted in low conversion and diastereoselectivities (entries 2 and 3, respectively). Phosphorous bases showed to be not compatible with our system, as moderate or no conversions were observed (entries 4-5). Tetraethylammonium bicarbonate, highly soluble in THF, showed a conversion of 74% but regretfully with a low diastereoselectivity (*syn*/*anti* = 66:34, entry 6). In sharp contrast, when Cs_2CO_3 was used, which is partially soluble in THF, slowly generating the reactive imine, good yield and excellent diastereo- and enantioselectivities were achieved (89%, *syn*/*anti* = 88:12; 93% *ee*, entry 7). Additionally, an increase of the number of equivalents of the base (from 1.2 to 1.5 equiv) resulted beneficial for the reaction rate (95%, *syn*/*anti* = 88:12; 90% *ee*, entry 8).

Table A.I: Evaluation of the base



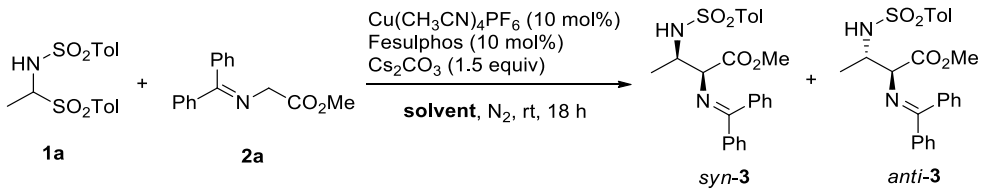
Entry	Base	**3** Yield (%)[a]	*syn*/*anti*[b]	*syn*-*ee* %[c]
1	Et_3N	-[d]	-	-
2	$(iPr)_2NH$	55	73:27	-
3	$(iPr)_2EtN$	38	75:25	-
4	K_3PO_4	59	83:17	-
5	$(NBu)_4PO_4H_2$	-[d]	-	
6	$(NEt)_4CO_3H$	74	66:34	-
7	Cs_2CO_3 (1.2 equiv)	89	88:12	93
8	Cs_2CO_3 (1.5 equiv)	95	88:12	90

[a] Conversion yields by ^1H NMR spectroscopy; [b] *syn*/*anti* ratio determined by ^1H NMR spectroscopy from the crude mixture; [c] The *ee* was measured by chiral HPLC only when both the conversion and the diastereoselectivities were good. [d] No reaction.

- ***Study of the solvent***

We next evaluated the role of the solvent, which plays a crucial role in stabilizing the intermediate species where the asymmetric induction is transferred to the final product (Table A.2). While other polar solvents, such as acetonitrile or trifluorotoluene resulted in a decrease of both the conversion and the diastereoselectivity (entries 2 and 3, respectively), DCM, an apolar non-coordinating solvent, completely shut down the reaction (entry 4).

Table A.2: Evaluation of the solvent



Entry	Solvent	**3** Yield (%)[a]	*syn*/*anti*[b]	*syn*-*ee* %[c]
1	THF	95	88:12	90
2	MeCN	53	79:21	-
3	trifluorotoluene	53	87:13	93
4	DCM	-[d]	83:17	-

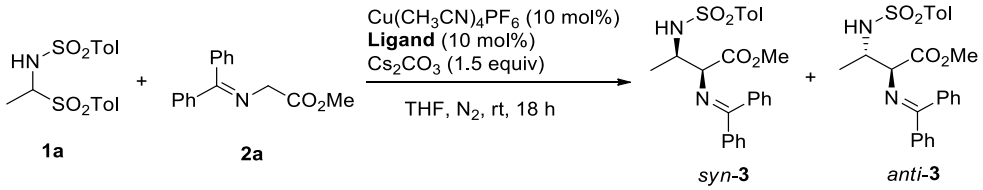
[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *syn*/*anti* ratio determined by ^{1}H NMR spectroscopy from the crude mixture; [c] The *ee* was measured by chiral HPLC only when both the conversion and the diastereoselectivities were good. [d] No reaction.

- ***Study of the ligand***

Para-substitution, with both electron-donating and withdrawing groups, in the phosphine aromatic rings of the Fesulphos ligand resulted in moderated yields and a slightly reduction of diastereoselectivity (entries 1-3). Josiphos ligand afforded moderate conversion (54%) with excellent diastereoisomeric ratio and enantioselectivity (*syn*/*anti* 92:8, 93% *ee*) (entry 4). However, when bulkier substituted ligands, such as Mandyphos, were used, a detrimental effect in the reaction rate was observed (23%, entry 5).

At this point, having stablished the Fesulphos as the optimal ligand for this transformation, we tested whether or not the conversion of the reaction would be affected by a reduction of the catalyst loading. Regretfully, when the CuI-Fesulphos catalyst loading was reduced to a 5 mol%, the reactivity of the reaction considerably diminished (52%, entry 6).

Table A.3: Evaluation of the ligand



Entry	Ligand	**3** Yield (%)[a]	*syn*/*anti*[b]	*syn-ee* %[c]
1	Fesulphos	95	88:12	90
2	Fesulphos *p*-F	67	84:16	94
3	Fesulphos *p*-OMe	74	86:14	88
4	Josiphos (R, S_p)	54	92:8	93
5	Mandyphos (R,S)	23	-	-
6	Fesulphos (5 mol%)	52	87:13	-

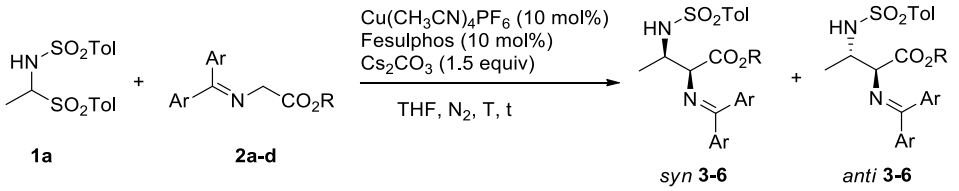
[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *syn*/*anti* ratio determined by ^{1}H NMR spectroscopy from the crude mixture; [c] The *ee* was measured by chiral HPLC only when both the conversion and the diastereoselectivities were good.

- ***Study of the electronic and steric nature of the glycine counterpart and the temperature***

Having established Cs_2CO_3 (1.5 equiv) and THF as the optimal base and solvent, in the presence of a 10 mol% of a combination of Fesulphos ligand and $Cu(CH_3CN)_4PF_6$, we next moved on to tune the electronic and steric nature of the glycine counterpart for further optimization. The model reaction was carried out at shorter reaction times (5 h) obtaining the expected product **3** in acceptable 52% yield and good stereocontrol (*syn*/*anti* = 88:12; 93% *ee,* entry 1).The sterically encumbered *tert*-butyl ester **2b** caused a positive impact on the yield (67%), as well as on the diastereo- and enantio-control (*syn*/*anti* = 96:4; 97% *ee*, entry 2). Instead, no further

improvement was observed by performing the reaction at -20 ºC for 18 h (entry 3). Regarding the electronic modification of the imine part of the glycinate,[293,294] better reactivity and stereocontrol was observed with the more electron-deficient 4,4´-dichlorobenzophenone **2c** (62% yield, *syn*/*anti* = >98:<2; 98% *ee* entry 4). To our delight, the 4,4´-difluorobenzophenone **2d**, remarkably improved the yield of the desired product **6** (74%), as well as both diastereo-(*syn*/*anti* = >98:<2) and enantiocontrol (>99% *ee*, entry 5).

Table A.4: Evaluation of the electronic and steric nature of the glycinate



Entry	R	Ar	T (ºC)	Yield (%)[a]	*syn*/*anti*[b]	*ee* %[c]
1[d]	Me	Ph (**2a**)	rt	52 (**3**)	88:12	93
2[d]	^{t}Bu	Ph (**2b**)	rt	67 (**4**)	96:4	97
3[e]	^{t}Bu	Ph (**2b**)	-20	40 (**4**)	96:4	97
4[e]	^{t}Bu	4-ClC_6H_4 (**2c**)	-20	62 (**5**)	>98:<2	98
5[e]	^{t}Bu	4-FC_6H_4 (**2d**)	-20	74 (**6**)	>98:<2	>99

[a] Isolated yield after chromatography; [b] *syn*/*anti* ratio determined by ^{1}H NMR spectroscopy from the crude mixture; [c] determined by chiral HPLC; [d] reaction time: 5 h; [e] reaction time: 18 h.

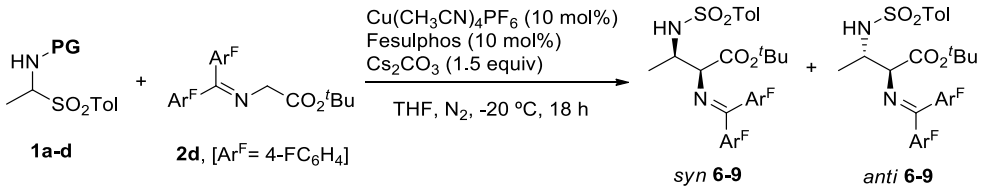
[293] Pioneering work by Kobayashi´s group has revealed that the nature of the imine pronucleophile can significantly influence its reactivity in Mannich-type reactions: S. Kobayashi, T. Tsubogo, S. Saito, Y. Yamashita, *Org. Lett.* **2008**, *10*, 807. See also reference 288.

[294] These electronically modified glycine Schiff bases were prepared following reported procedures, see reference 291.

- ***Study of the protecting group of the α-amido sulfone***[295]

The reaction also demonstrated high sensitivity to the nature of the *N*-protecting group at the α-amido sulfone (Table A.5). The *N*-Boc-protected substrate **1b** failed to react with **2d** (entry 2). *N*-arylsulfonyl α-amido sulfones such as those with *p*-nosyl (**1c**) or (2-naphthyl)sulfonyl (**1d**) groups, participated in the Mannich reaction, albeit with lower efficiency than the parent substrate **1a** (32% and 54% yield, respectively; entries 3 and 4). In all the cases, the α-amido sulfones **1a-d** were completely consumed in the reaction, suggesting that the lower yield in the latter examples is due to the competing decomposition of the *in situ* generated reactive imine.

Table A.5: Evaluation of the α-amido sulfone protecting group



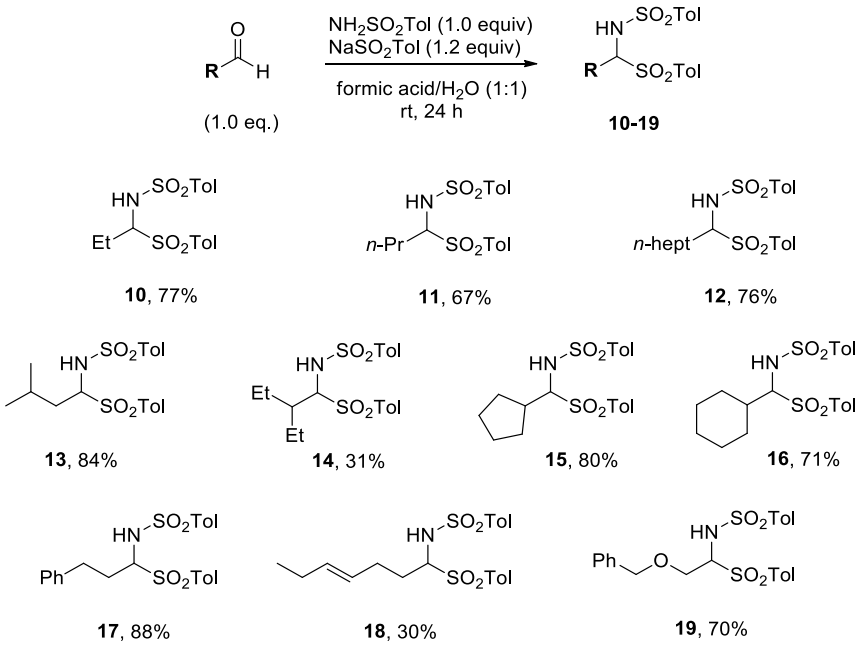
Entry	PG	Yield (%)[a]	syn/anti[b]	*syn-ee* %[c]
1	Ts (**1a**)	74 (**6**)	>98:<2	>99
2	Boc (**1b**)	- (**7**)[d]	-	-
3	*p*-Ns (**1c**)	32 (**8**)	>98:<2	97
4	2-NaphSO_2 (**1d**)	54 (**9**)	>98:<2	97

[a] Conversion yields by ^{1}H NMR spectroscopy; [b] *syn*/*anti* ratio determined by ^{1}H NMR spectroscopy from the crude mixture; [c] determined by chiral HPLC; [d] No reaction.

[295] Substrates **1a-d** were prepared following the typical *N*-protection protocols described previously in this Thesis manuscript.

A.3.2 Structural versatility of the asymmetric glycinate Mannich reaction

The versatility of the reaction with regard to modifications in the α-amido sulfone moiety was studied. For that purpose, a variety of differently substituted aliphatic α-amido sulfones were synthesized following the standard protocol from the corresponding commercially available aldehydes.[290]

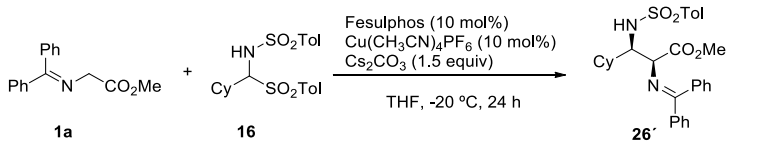


Scheme A.10

This set of α-amido sulfones were then subjected to the optimized reaction conditions, achieving the expected amino acid derivatives with high yields (typically >70%) and excellent diastero- and enantio-selectivities. Linear alkyl groups, regardless of the length of the chain (products **20**-**22**, 92-98% *de*, 96-99% *ee*), as well as sterically more demanding side chains branched at the α- or β-position, irrespective of the acyclic (isobutyl, 2-pentyl) or cyclic (cyclopentyl, cyclohexyl) nature

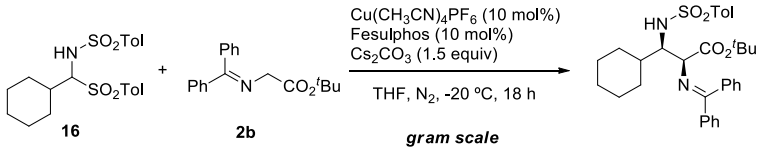
of the substituent (**23**-**26**, *syn*/*anti* = 96:4->99:<1, 97-99% *ee*),[296] were accommodated with no impact on yield or stereocontrol. Amido sulfones containing functional groups (aryl, alkene or benzyloxy) also behaved very well (**27**-**29**, *syn*/*anti* = 90:10-96:4, 93-99% *ee*), providing useful compounds for further manipulation. To demonstrate the practicality of the protocol, the reaction of cyclohexyl-substituted amido sulfone **16** with glycinate **2d** was ten-fold scaled up (1.5 mmol) without significant loss of chemical or stereochemical efficiency (product **26**, 80% yield, *syn*/*anti* = 98:2, 96% *ee*).[297]

[296] The relative and absolute configuration of the Manich products was determined by preparation of known **26´** (methyl ester derivative of product **26**) and comparison of the NMR data and optical rotation value. See reference 276.

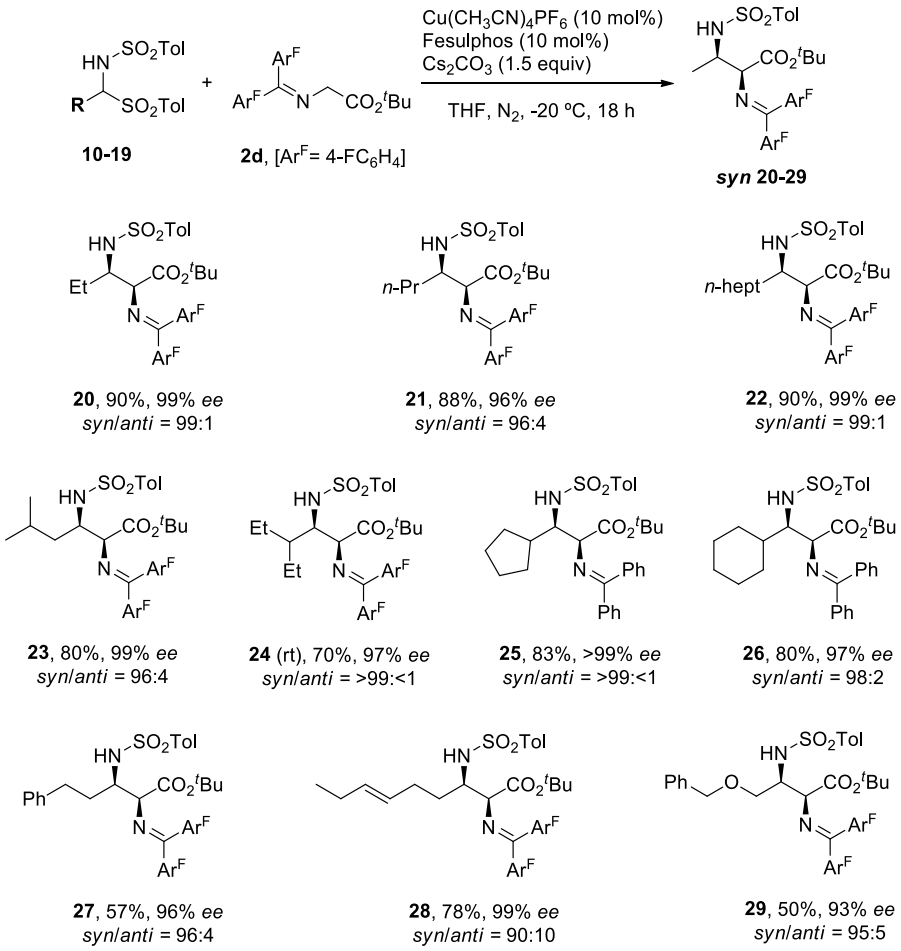


$[\alpha]_D^{25}$ obs. = -38 (c = 0.9, $CHCl_3$)
$[\alpha]_D^{25}$ lit. = -39 (c = 1.0, $CHCl_3$)

[297] The scale-up of the reaction is shown in Scheme bellow.



26, 80%, 96% *ee*
syn/*anti* = 98:2

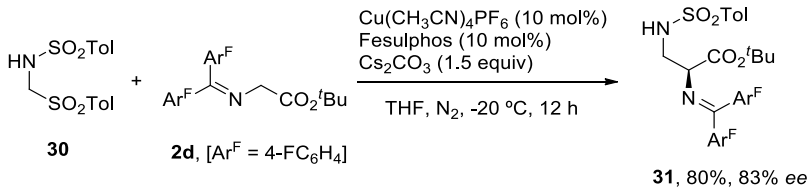


Scheme A.11

We next focussed our attention on formaldehyde derived α-amido sulfone **30**, because formaldehyde does not form stable imines and because optically active 2,3-diamino-propanoic acid derivatives display various biological activities.[298] Notably, the Mannich reaction of **30** with glycinate **2d** enabled a practical and straightforward method for α-aminomethylation of glycine derivatives (product **31**, 80% yield, 83%

[298] G. Kumaraswamy, A. Pitchaiah, *Helv. Chim. Acta*, **2011**, *94*, 1543.

ee). To the best of our knowledge, neither the use of formaldehyde α-amido sulfones in catalytic asymmetric Mannich reaction nor the asymmetric aminomethylation of glycine derivatives has been documented.[299]



Scheme A.12

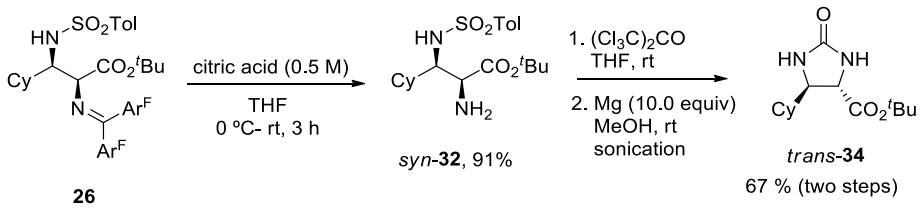
A.3.3 Amino-deprotection and synthetic application

The sequential double amino deprotection of the Mannich adduct **26** and its transformation into the optically active imidazolidinone *trans*-**34**, which also served to confirm otherwise the *syn*-configuration of **26**, is depicted in Scheme A.8.[300]

Treatment of **26** with a 0.5 M solution of citric acid in THF, efficiently hydrolyzed the glycinate imine yielding free amino derivative *syn*-**32** in 91% yield after just 2 hours at room temperature. Further reaction of *syn*-**32** with triphosgene provided cyclized *trans*-**33**, which could be smoothly deprotected in the presence of Mg turnings under sonication, achieving the desired *trans*-**34** (67% for two steps).

[299] For previous catalytic asymmetric Mannich reactions with formaldehyde-derived imines or iminium ions, see: a) I. Ibrahem, W. Zou, J. Casas, H. Sundén, A. Córdova, *Tetrahedron*, **2006**, *62*, 357. b) Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2006**, *128*, 6804. c) I. Ibrahem, J. Casas, A. Córdova, *Angew. Chem. Int. Ed.* **2004**, *43*, 6528.

[300] For *cis*- and *trans*-assignment on imidazolidinones derived from α,β-aminoacid derivatives, see: S. H. Lee, J. Yoon, S. H. Chung, Y. S. Lee, *Tetrahedron*, **2001**, *62*, 2139.



Scheme A.13

A.3.4 Stereochemical model

As in our previous results from aryl aldimines,[288] the high enantio- and diastereoselectivity observed in favour of the products *syn*-(2*S*,3*R*)-configuration can be explained assuming the participation of the *Z*-enolate **I**[301] as the catalytically active nucleophile. In this complex, the high steric congestion imposed by the *tert*-butyl group at the sulphur atom in close proximity to the copper center hinders the approach of the *N*-sulfonyl imine from the *Re* C-α enolate face of the azomethine. Thus, the approach of **I** from the more accessible *Si* C-α enolate face to the *N*-sulfonyl imine accounts for the high stereoselectivity attained in the formation of the C(2*S*) sterecenter (TS-**II**).

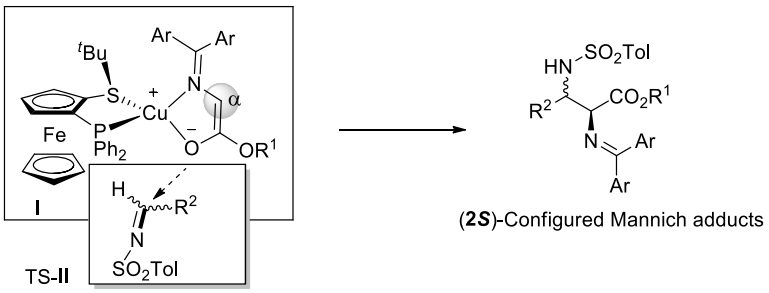


Figure A.2

[301] The complex **I** was found to be the most stable geometry in the coordination of the metal atom with the Fesulphos and the azomethine species, see reference 288b.

The high *syn*-diastereocontrol can be tentatively rationalized invoking a severe steric repulsion of the bulky *N*-diarylmethylene group in the ketamine nucleophile with the *N*-sulfonyl group,[276,288] thereby, disfavouring **IIIa** (leading to *anti*-configured products) and forcing the imine approach from its *Si*-face *via* intermediate **IIIb** that would account for the formation of the *syn*-(2*S*,3*R*)-adducts.

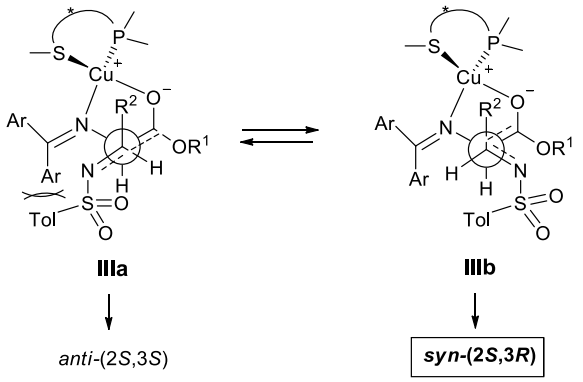
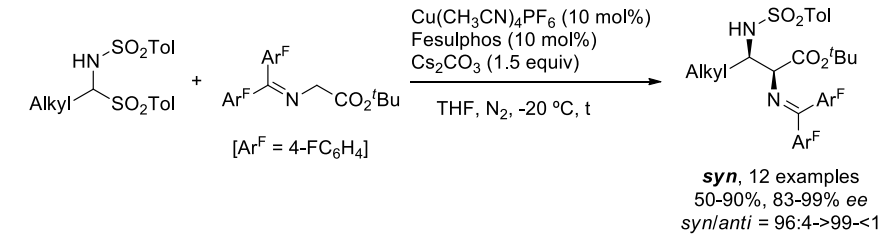
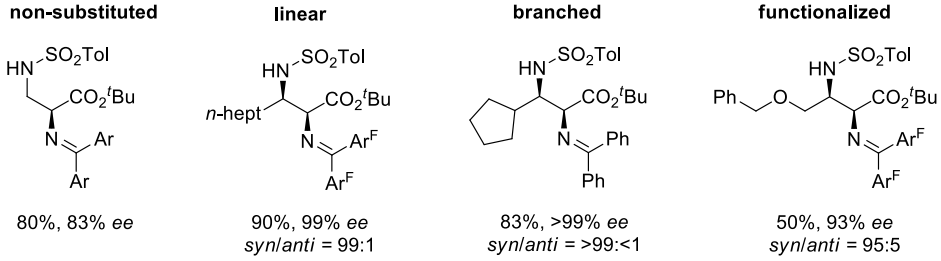


Figure A.3

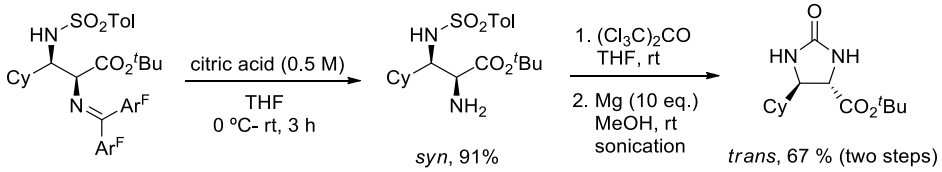
A.4 Conclusions

In conclusion, an efficient and practical asymmetric Cu^{I}-catalyzed Mannich reaction of glycine derivatives with aliphatic imines, generated *in situ* from their corresponding α-amido sulfones has been devised. β-alkyl-α,β-diamino acid derivatives are produced in good yields and excellent diastereo- and enantiocontrol (typically, *syn*/*anti* = >90:<10 and >90% *ee*).



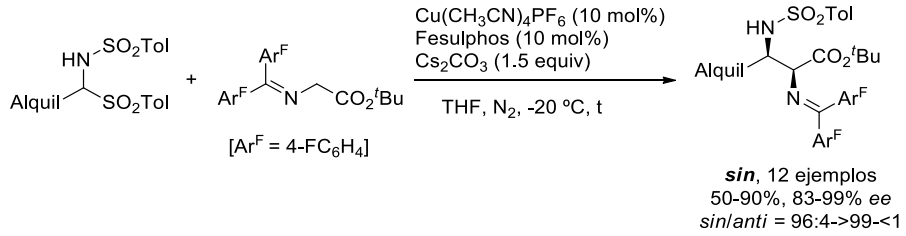


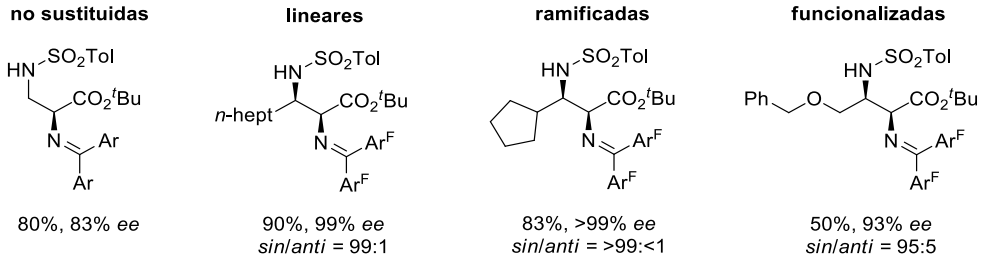
The selective orthogonal *N*-deprotection under mild conditions as well as the generation of optically active *trans*-imidazolidinones, was also demonstrated.



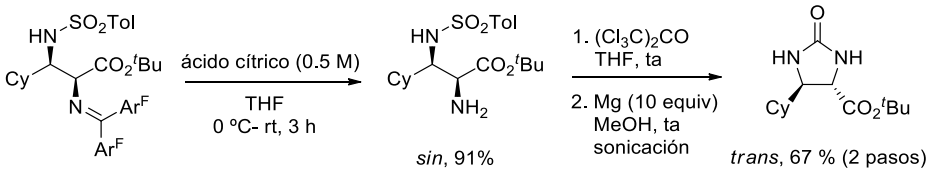
A.4. Conclusiones

Se ha desarrollado una nueva metodología para la reacción de Mannich asimétrica entre derivados de glicina y aminas alifáticas, las cuales fueron generadas *in situ* a partir de sus correspondientes α-amido sulfonas, catalizada por el sistema Cu^{I}-Fesulphos. Los productos de reacción, derivados de β-alquila-α,β-diamino ácidos, fueron sintetizados con buenos rendimientos y con excelentes diastero- y enantio-selectividades (típicamente, *sin*/*anti* = >90:<10 y >90% *ee*).





Los dos grupos aminos diferentemente protegidos pudieron ser selectivamente desprotegidos bajo condiciones suaves de reacción, tal y como se demostró en la síntesis de *trans*-imidazolinonas ópticamente activas.



A.5. Experimental section.

A.5.1. Synthesis of the Fesulphos ligand

(R_s)-*tert*-Butylsulfinylferrocene I.[302] To a suspension of ferrocene (3.01 g, 16.18 mmol) in THF (7.5 mL), cooled to 0 ºC, was added dropwise a 1.7 M solution of ^{t}BuLi in dry pentane (9.8 mL, 16.70 mmol). The reaction was stirred at 0 ºC for 20 min and it was diluted with pentane (25 mL). To the resulting mixture was slowly added a solution of a 87% *ee* sample of (*R*)-S-*tert*-butyl *tert*-butanethiosulfinate[303] (1.55 g, 7.97 mmol) in pentane (5.0 mL) at 0 ºC. The mixture was stirred at 0 ºC for 1 h and then brine (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane-EtOAc 1:2) to afford sulfoxide (*R*)-**I** (1.70 g, 73%) with 87% *ee*, as a yellow-orange solid. A single recrystallization from CH_2Cl_2-hexane (1:1) afforded (*R*)-**I**; yield: 1.02 g (60%) with >99% **ee**; mp = 150-151 ºC (Lit.[302] mp = 149-150 ºC). **^{1}H NMR (300MHz, Chloroform-*d*)** δ (ppm): 4.68 (m, 1H), 4.41 (m, 2H), 4.38 (s, 5H), 4.35 (m, 1H), 1.12 (s, 9H). **$[\alpha]_D^{20}$** = -355 (*c* = 0.5, $CHCl_3$) {Lit.[302] $[\alpha]_D^{20}$= -339 (*c* = 0.5, $CHCl_3$), 95% *ee*}. HPLC: Daicel Chiralpak AS, *i*-PrOH/hexane 3/97, flow rate 1.0 mL/min (λ= 210.0 nm), τ: 6.5 min (*S)* and 7.9 min (*R).*

(R_{Fc}, R_S)-1-(*tert*-Butylsulfinyl)-2-(diphenylphosphino)ferrocene II. To a solution of sulfoxide (*R*)-**I** (700 mg, 2.41 mmol) in THF (24 mL) was added a 1.7 M solution of ^{t}BuLi in pentane (2.1 mL, 3.62 mmol). The mixture was stirred at -78 ºC for 1.5 h and then chlorodiphenylphosphine (0.60 mL, 3.62 mmol) was added at -78 ºC. The reaction mixture

[302] a) N. M. Lagneau, Y. Chen, P. M. Robben, H. -S. Sin, K. Takasu, J. -S. Chen, P. D. Robinson, D. H. Hua, *Tetrahedron,* **1998**, *54*, 7301. b) P. Diter, O. Samuel, S. Taudien, H. B. Kagan, *Tetrahedron: Asymmetry,* **1994**, *5*, 549.

[303] D. A. Cogan, G. Liu, K. Kim, B. J. Backes, J. A. Ellman, *J. Am. Chem. Soc.* **1998**, *120*, 8011.

was stirred for 30 min and it was quenched with water (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/EtOAc 1:1) affording (*R*)-**II** as a yellow solid; yield; 1.01 g (91%); m.p = 162-163 ºC (Lit.[304] m.p = 162-163 ºC). **^{1}H NMR (300MHz, Chloroform-*d*)** δ (ppm): 7.61 – 7.52 (m, 2H), 7.35 – 7.28 (m, 3H,), 7.27 – 7.14 (m, 5H), 4.60 – 4.56 (m, 1H), 4.53 – 4.48 (m, 1H), 4.22 – 4.18 (m, 1H), 4.10 (s, 5H), 0.98 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 140.6, 140.4, 138.8, 138.6, 135.8, 135.5, 132.9, 132.7, 129.2, 128.1, 127.9, 127.8, 90.1, 89.8, 76.5, 76.2, 75.3, 75.2, 74.0, 72.5, 71.5, 55.9, 23.7. **MS** m/z 474 (M^+, 13), 418 (91), 352 (100), 228 (25), 170 (22). **Elemental analysis**: calcd. for $C_{26}H_{27}FeNOPS$: C, 65.83, H, 5.74, N, 6.76; Found: C, 65.64, H, 5.78, N, 6.26.

(R_{Fc})-1-(*tert*-Butylsulfenyl)-2-(diphenylphosphino)ferrocene (Fesulphos). To a solution of sulfoxide (*R*)-**II** (1.10 mmol) in toluene (12 mL), were successively added Et_3N (2.3 mL, 16.50 mmol) and $HSiCl_3$ (1.10 mL, 11.00 mmol). The mixture was refluxed for 12 h and then it was poored into a mixture of CH_2Cl_2 (35 mL) and 10% aqueous 2 M of NaOH (40 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvents were evaporated. The residue was purified by flash chromatography (*n*-hexane/EtOAc 5:1), affording **Fesulphos** as an orange solid; yield: 575 mg (89%); m.p = 148-149 ºC. **^{1}H NMR (300MHz, Chloroform-*d*)** δ (ppm): 7.68 – 7.58 (m, 2H), 7.39 – 7.28 (m, 5H), 7.28 – 7.20 (m, 3H), 4.71 – 4.67 (m, 1H), 4.50 – 4.46 (m, 1H), 4.15 – 4.12 (m, 1H), 3.98 (s, 5H), 1.00 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 139.9, 138.3, 135.3, 135.0, 133.0, 132.7, 128.9, 127.9, 83.1, 81.0, 80.0, 73.4, 71.5, 70.6, 46.0, 31.0. **MS** *m/z* 458 (M^+, 95), 402 (100), 337 (52), 302 (11), 217 (27), 170 (31), 121 (10). **Elemental analysis**: calcd. $C_{26}H_{27}FePS$: C, 68.17; H, 5.94; S,

[304] O. Riant, G. Argouarch, D. Guillaneux, O. Samuel, H. B. Kagan, *J. Org. Chem.,* **1998**, *63*, 3511.

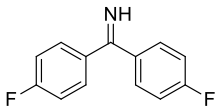
7.00. Found: C, 67.78; H, 6.10; S, 6.75. **ee** = >99%. **$[\alpha]_D^{20}$** = -200 (*c* = 0.5, $CHCl_3$). HPLC: Daicel Chiralpak OD, *i*-PrOH/hexane 0.8/99.2, flow rate 0.5 mL/min (λ= 210.0 nm), τ: 22.0 min (*R)* and 26.1 min (*S).*

A.5.2. Synthesis of glycine Schiff bases

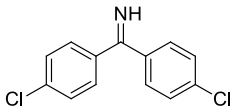
- ***Synthesis of substituted-benzophenone imines***[291a]

Typical procedure A.1: To a solution of the corresponding substituted benzophenone derivative (8.00 mmol) in dry toluene (40 mL) at 0 ºC, were added 12.00 mmol of $TiCl_4$ and the solution was stirred at that temperature for 10 min. Then, gaseous ammonia was bubbled through the solution for 10 min causing a colour change. The resulting mixture was warmed up to rt and stirred for 24 h. The reaction was quenched by pouring 50 mL of a (sat.) Na_2CO_3 solution, subsequent stirring for 1 h at rt. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). All the organic phases were combined, washed with (sat.) Na_2CO_3 (1 x 20 mL) and brine (1 x 20 mL) and dried over $MgSO_4$. After solvent evaporation, the product was triturated in hexane and if necessary recrystallized in MeCN, yielding the expected substituted-benzophenone imines.

Bis(4-fluorophenyl)methanimine (imine 1). Following the typical procedure A.1, the reaction of 4,4´-*para*-fluorobenzophenone (1.76 g, 8.00 mmol) with $TiCl_4$ (1.32 mL, 12.00 mmol) and ammonia, afforded a dark yellow oil; yied: 1.60 g (92%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.17 (t, *J* = 8.7 Hz, 4H); 7.50 – 7.70 (m, 4H); 9.68 (s, 1H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 115.3; 115.5; 130.4; 130.5; 135.3; 162.4; 165.7; 175.8.



Bis(4-chlorophenyl)methanimine (imine 2). Following the typical procedure A.1, the reaction of 4,4´-*para*-chlorobenzophenone (2.03 g, 8.00 mmol) with $TiCl_4$ (1.32 mL, 12.00 mmol) and ammonia, afforded a dark yellow oil; yied: 1.79 g (90%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.17 – 7.49 (m, 7H); 7.66

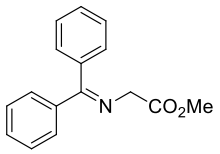


(d, *J* = 8.4 Hz, 1H); 9.69 (s, 1H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 128.8; 129.7; 131.3; 136.8; 176.1.

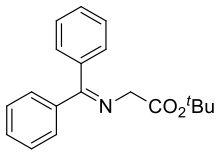
- ***Synthesis of glycine Schiff base derivatives***[291b]

Typical procedure A.2: To a mixture of the corresponding diarylmethanimine (10.0 mmol) and the corresponding glycine alkyl ester (10.0 mmol) in dry DCM (50 mL), was added $MgSO_4$ (15.0 mmol). The reaction mixture was stirred at room temperature for 24 hours, then it was filtered, washed with brine (3 x 20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, yielding the corresponding glycine Schiff base without any further purification.

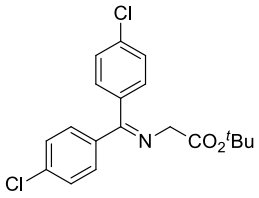
Methyl-2-(diphenylmethyleneamino)acetate (2a). Following the typical procedure A.2, the reaction of benzophenone imine (1.91 g, 10.00 mmol) with glycine methyl ester hydrochloride (1.39 g, 11.00 mmol) afforded the iminoester **2a** as a pale yellow solid; yield: 2.41 g (95%); mp = 42-43 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.53 – 7.49 (m, 2H), 7.28 – 7.23 (m, 3H), 7.18 – 7.08 (m, 3H), 6.99 – 6.95 (m, 2H), 4.05 (s, 2H), 3.51 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.2, 170.4, 138.8, 135.5, 130.0, 128.4, 128.3, 128.2, 127.6, 127.1, 55.1, 51.4.



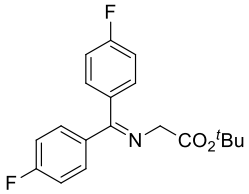
***tert*-Butyl-2-(diphenylmethyleneamino)acetate (2b).** Following the typical procedure A.2, the reaction of benzophenone imine (1.91 g, 10.00 mmol) with glycine *tert*-butyl ester hydrochloride (1.84 g, 11.00 mmol) afforded the iminoester **2b** as a white solid; yield: 2.71 g (92%); mp = 112-113 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.69 – 7.64 (m, 2H), 7.47 – 7.43 (m, 3H), 7.39 – 7.30 (m, 3H), 7.20 – 7.17 (m, 2H), 4.12 (s, 2H), 1.46 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.4, 169.8, 139.4, 136.2, 130.3, 128.7, 128.6, 128.5, 128.0, 127.7, 81.0, 56.3, 28.1. **HRMS-FAB^{+}** calcd. for $C_{19}H_{21}NO_2$ $(M)^{+}$: 295.1572; Found: 295.1568. **Elemental analysis** calcd. for $C_{19}H_{21}NO_2$: C, 77.26, H, 7.17, N, 4.74; Found: C, 77.29, H, 7.13, N, 4.71



***tert*-Butyl-2-(bis(4-chlorophenyl)methyleneamino)acetate (2c).** Following the typical procedure A.2, the reaction of bis(4-chlorophenyl)methanimine (2.50 g, 10.0 mmol) with glycine *tert*-butyl ester hydrochloride (1.84 g, 11.0 mmol) afforded the iminoester **2c** as a white solid; yield: 3.23 g (89%); mp = 88-89 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.57 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 4.08 (s, 2H), 1.45 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 169.4, 169.2, 137.5, 136.8, 135.1, 133.9, 130.0, 129.2, 129.1, 128.4, 81.4, 56.3, 28.1. **HRMS-FAB$^+$** calcd. for $C_{19}H_{19}Cl_2NO_2$ $(M)^+$: 363.0793; Found: 363.0804. **Elemental analysis** calcd for $C_{19}H_{19}Cl_2NO_2$: C, 62,65, H, 5.26, N, 3.85; Found: C, 62.34, H, 5.25, N, 3.73.



***tert*-Butyl-2-(bis(4-fluorophenyl)methyleneamino)acetate (2d).** Following the typical procedure A.2, the reaction of bis(4-fluorophenyl)methanimine (2.17 g, 10.0 mmol) with glycine *tert*-butyl ester hydrochloride (1.84 g, 11.0 mmol) afforded the iminoester **2d** as a white solid; yield: 2.81 g (86%); mp = 84-85 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.66 – 7.58 (m, 2H), 7.17 – 7.10 (m, 4H), 7.02 – 6.93 (m, 2H), 4.08 (s, 2H), 1.44 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 169.4, 169.2, 165.9, 164.4, 162.5, 161.1, 135.5, 135.4, 131.6, 131.5, 130.7, 130.6, 129.7, 129.6, 115.9, 115.6, 115.1, 114.8, 81.1, 56.1, 27.9. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -110.3, -111.6. **HRMS-FAB$^+$** calcd. for $C_{19}H_{19}F_2NO_2$ $(M)^+$: 331.1384; Found: 331.1372. Elemental analysis calcd for $C_{19}H_{19}F_2NO_2$: C, 68.87, H, 5.78, N, 4.23; Found: C, 68.83, H, 5.78, N, 4.23.



A.5.3. Synthesis of aliphatic α-amido sulfones[290]

Typical procedeure A.3: To a solution of sulfonamide (1.0 equiv) and $TolSO_2Na$ (1.2 equiv) in a formic acid/H_2O 1:1 mixture (30 mL), cooled to 0 ºC, was added the corresponding aliphatic aldehyde (1.0 equiv). The solution was warmed up to rt and

stirred for 24 h, whereupon a white solid precipitated. The white powder was successively washed with water and pentane, and then air-dried to give the corresponding *α*-amido sulfone.

4-Methyl-*N*-(1-tosylethyl)benzenesulfonamide (1a). Following the typical procedure A.3, the reaction of acetaldehyde (0.56 mL, 10.00 mmol) with *p*-toluensulfonamide (1.71 g, 10.00 mmol) and $TolSO_2Na$ (1.97 g, 12.0 mmol), afforded **1a** as a white solid; yield: 3.18 g (90%); m.p = 114-116 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.77 (d, *J* = 8.1 Hz, 2H), 7,58 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 5.78 (d, *J* = 9.8 Hz, 1H), 4.47 – 4.45 (m, 1H), 2.48 (s, 3H), 2.44 (s, 3H), 1.49 (d, *J* = 6.8 Hz. 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.4, 143.4, 137.3, 132.3, 129.7, 129.6, 126.8, 69.4, 21.8, 21.6, 14.3. **HRMS-ESI** calcd. for $C_9H_{12}NO_2S$ (M-*p*$TolSO_2$+H)$^+$: 198.0590; Found: 198.0576. **Elemental analysis**: calcd for $C_{16}H_{19}NO_4S_2$: C, 54.37; H, 5.42; N, 3.96; S, 18.14. Found: C, 54.48; H; 5.37; N, 3.92; S, 18.08.

***tert*-Butyl-(1-tosylethyl)carbamate (1b).**[305] *tert*-Butyl carbamate (0.69 g, 5.94 mmol) and $TolSO_2Na$ (2.17 g, 11.88 mmol) were dissolved in a MeOH/H_2O 1:2 mixture (20 mL) and it was cooled to 0 ºC. Then acetaldehyde (0.50 mL, 8.91 mmol) was successively added subsequent addition of formic acid (0.41 mL). The solution was then warmed up to rt and stirred for 24 h, whereupon a white solid precipitated. The white powder was successively washed with water, diethyl ether and pentane, to give **1b** as white solid; yield: 1.41 g (80%); m.p = 110-111 ºC. **^{1}H NMR (300MHz, Chloroform-*d*)** δ (ppm): 7.83 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 2H), 5.14 – 4.89 (m, 2H), 2.46 (s, 3H); 1.64 (d, *J* = 6.6 Hz, 3H), 1.26 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 153.6, 144.8, 133.6, 129.6, 129.4, 80.4, 66.9, 27.9, 21.5, 12.8. **HRMS-ESI** calcd. for $C_{14}H_{21}NNaO_4S$ (M+Na)$^+$: 322.1083; Found: 322.1089. Calcd. For $C_{28}H_{42}N_2NaO_8S_2$ (2M+Na)$^+$: 621.2280; Found: 621.2276.

[305] H. Zhang, S. Syed, Carlos F. Barbas III, *Org. Lett.* **2010**, *12*, 708.

4-Nitro-*N*-(1-tosylethyl)benzenesulfonamide (1c). Following the typical procedure A.3, the reaction of acetaldehyde (0.22 mL, 3.87 mmol) 4-nitrobenzenesulfonamide (0.52 g, 2.58 mmol) and $TolSO_2Na$ (0.93 g, 5.17 mmol), afforded **1c** as a white solid; yield: 0.70 g (71%); m.p = 135-137 ºC. **^{1}H NMR (300 MHz, Acetone-*d*$_6$)** δ (ppm): 8.36 (d, *J* = 8.9 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.82 (d,*J* = 9.4 Hz, 1H), 7.68 (d, *J* = 8.2, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 4.85 (dd, *J* = 10.0, 6.8 Hz, 1H), 2.42 (s, 3H), 1.46 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (75 MHz, Acetone-*d*$_6$)** δ (ppm): 150.9, 147.6, 146.0, 134.2, 130.5, 130.4, 129.0, 125.2, 70.3, 21.5, 14.9. **HRMS-ESI** calcd. for $C_{15}H_{16}N_2NaO_6S_2$ ($M+Na^+$): 407.0342; Found: 407.0332. Calcd. for $C_{30}H_{32}N_4Na_2O_{12}S_4$ ($2M+Na^+$): 791.0747; Found: 791.0822.

***N*-(1-Tosylethyl)naphthalene-2-sulfonamide (1d).** Following the typical procedure A.3, the reaction of acetaldehyde (0.20 mL, 3.62 mmol) with naphthalene-2-sulfonamide (0.50 g, 2.41 mmol) and $TolSO_2Na$ (0.86 g, 4.82 mmol) afforded **1d** as a white solid; yield: 0.63 g (67%); m.p = 118-119 ºC. **^{1}H NMR (300MHz, Chloroform-*d*)** δ (ppm): 8.46 – 8.39 (m, 1H), 8.11 – 8.03 (m, 2H), 7.99 – 7.93 (m, 1H), 7.78-7.59 (m, 2H), 7.50 – 7.40 (m, 3H), 6.90 (d, *J* = 8.1 Hz, 2H), 5.44 – 5.25 (m, 1H), 4.67-4.49 (m, 1H), 2.33 (s, 3H), 1.56 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 144.8, 134.6, 134.4, 134.1, 132.1, 129.2, 129.0, 128.9, 128.6, 127.7, 127.0, 124.2, 124.0, 69.4, 21.7, 14.9. **HRMS-ESI** calcd. for $C_{19}H_{19}NNaO_4S_2$ $(M+Na)^+$: 412.0647; Found: 412.0648. Calcd. for $C_{38}H_{38}N_2NaO_8S_4$ $(2M+Na)^+$: 801.1409; Found: 801.1448.

4-Methyl-*N*-(1-tosylpropyl)benzenesulfonamide (10). Following the typical procedure A.3, the reaction of propionaldehyde (0.73 mL, 10.00 mmol) with *p*-toluenesulfonamide (1.71 g, 10.00 mmol) and $TolSO_2Na$ (1.97 g, 12.00 mmol) afforded **10** as a white solid; yield 2.84 g (77%); m.p = 118-120 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.73 (d, *J* = 8.3 Hz, 2H), 7,58 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 5.33 (d, *J* = 9.7 Hz, 1H), 4.43 (dt, *J* = 4.0 Hz, *J* = 10.0, 1H), 2.48 (s, 3H), 2.45 (s,

3H), 2.37 – 2.25 (m, 1H), 1.76-1.74 (m, 1H), 0.91 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.2, 143.6, 137.9, 132.9, 129.7, 129.6, 129.6, 126.7, 75.0, 21.9, 21.8, 21.6, 9.8. **HRMS-ESI** calcd. for $C_{10}H_{14}NO_2S$ (M-*p*TolSO$_2$+H)$^+$: 212.0747. Found: 212.0742. Calcd. for $C_{11}H_{17}NNaO_3S$ (M-*p*TolSO$_2$+Na+MeO$^-$)$^+$: 266.0827; Found: 266.0837.

4-Methyl-*N*-(1-tosylbutyl)benzenesulfonamide (11). Following the typical procedure A.3, the reaction of butyraldehyde (0.90 mL, 10.00 mmol) with *p*-toluenesulfonamide (1.71 g, 10.00 mmol) and TolSO$_2$Na (1.97 g, 12.0 mmol) afforded **11** as a white solid; yield: 2.58 g (67%); m.p = 119-120 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.70 (d, *J* = 8.3 Hz, 2H); 7,57 (d, *J* = 8.3 Hz, 2H); 7.30 (d, *J* = 8.1 Hz, 2H); 7.23 (d, *J* = 8.1 Hz, 2H); 5.35 (d, *J* = 10.4 Hz, 1H), 4.61 (dt, *J* = 10.2 Hz, *J* = 3.6, 1H); 2.47 (s, 3H); 2.45 (s, 3H); 2.16 – 2.13 (m, 1H); 1.69 – 1.67 (m, 1H); 1.41-1.39 (m, 1H); 1.27 – 1.25 (m, 1H); 0.86 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.3, 143.6, 137.9, 132.9, 129.7, 129.6, 126.8, 126.5, 73.7, 30.4, 21.8, 21.6, 18.5, 13.5. **HRMS-ESI** calcd. for $C_{11}H_{16}NO_2S$ (M-pTolSO$_2$+H)$^+$: 226.0902. Found: 226.0895. Calcd. for $C_{12}H_{19}NNaO_3S$ (M-pTolSO$_2$+Na+MeO$^-$)$^+$: 280.0983; Found: 280.0983.

4-Methyl-*N*-(1-tosyloctyl)benzenesulfonamide (12). Following the typical procedure A.3, the reaction of octanal (1.5 mL, 9.59 mmol) with *p*-toluenesulfonamide (1.67 g, 9.59 mmol) and TolSO$_2$Na (2.09 g, 11.51 mmol) afforded **12** as a white solid; yield: 3.30 g (76%); m.p = 112-113 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.76 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 5.51 (d, *J* = 9.8 Hz, 1H), 4.57 (dt, *J* = 10.2 Hz, *J* = 3.6 Hz, 1H), 2.48 (s, 3H), 2.44 (s, 3H), 2.17 – 2.14 (m, 1H), 1.69 – 1.66 (m, 1H), 1.40 – 1.00 (m, 10 H), 0.89 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.3, 143.6, 138.0, 132.8, 129.7, 129.6, 126.8, 73.9, 31.5, 28.9, 28.8, 28.2, 25.1, 22.6, 21.8, 21.5, 14.0. **HRMS-ESI** calcd. for $C_{15}H_{24}NO_2S$ (M-pTolSO$_2$+H)$^+$: 282.1522; Found: 282.1520. Calcd. for (M-pTolSO$_2$+Na+MeO$^-$)$^+$: calculated $C_{16}H_{27}NNaO_3S$: 336.1616; Found: 336.1620.

4-Methyl-*N*-(3-methyl-1-tosylbutyl)benzenesulfonamide (13). Following the typical procedure A.3, the reaction of 3-methyl-butyraldehyde (1.10 mL, 10.00 mmol) with *p*-toluenesulfonamide (1.71 g, 10.00 mmol) and $TolSO_2Na$ (1.97 g, 12.00 mmol) afforded **13** as a white solid; yield: 3.40 g (84%). m.p = 122-123 ºC; **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.58 (d, *J* = 8.3 Hz, 2H), 7,47 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 4.84 (d, *J* = 9.4 Hz, 1H), 4.61 (dt, *J* = 10.5 Hz, *J* = 3.7 Hz, 1H), 2.37 (s, 3H); 2.35 (s, 3H), 1.90 – 1.87 (m, 1H), 1.53 – 1.51 (m, 2H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.77 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.3, 143.6, 138.0, 132.7, 129.7(4), 129.7(1), 129.5, 126.8, 72.6, 37.4, 24.1, 23.3, 21.8, 21.6, 21.1. **HRMS-ESI** calcd. for $C_{12}H_{18}NO_2S$ $(M\text{-}pTolSO_2+H)^+$: 240.1058. Found: 240.1056. Calcd. for $C_{13}H_{21}NNaO_3S$ $(M\text{-}pTolSO_2+Na+MeO^-)^+$: 294.1140; Found: 294.1126. **Elemental analysis**: calcd. for $C_{19}H_{25}NO_4S_2$: C, 57.69; H, 6.37; N, 3.54; S, 16.21. Found: C, 57.64; H; 6.31; N, 3.49; S, 16.24.

***N*-(2-Ethyl-1-tosylbutyl)-4-methylbenzenesulfonamide (14).** Following the typical procedure A.3, the reaction of 2-ethylbutanal (1.0 mL, 8.83 mmol) with *p*-toluenesulfonamide (1.51 g, 8.83 mmol) and $TolSO_2Na$ (1.89 g, 10.61 mmol) afforded **14** as a white solid; yield: 1.10 g (31%); m.p = 56-57 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.61 (d, *J* = 8.3 Hz, 2H); 7.44 (d, *J* = 8.3 Hz, 2H); 7.24 – 7.16 (m, 2H); 7.11 (d, *J* = 8.1 Hz, 2H); 5.14 (d, *J* = 10.6 Hz, 1H); 4.60 (dd, *J* = 10.6 Hz, *J* = 1.9 Hz, 1H); 2.37 (s, 3H); 2.34 (s, 3H); 2.03 – 1.92 (m, 1H); 1.82-1.68 (m, 1H); 1.51-1.37 (m, 1H); 1.11 – 0.93 (m, 2H); 0.92 – 0.83 (t, *J* = 7.2 Hz, 3H); 0.83 – 0.74 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.0, 143.6, 138.1, 134.3, 129.7, 129.5, 129.2, 126.6, 74.4, 41.6, 22.8, 22.0, 21.7, 21.6 11.9, 11.7. **HRMS-ESI** calcd. for $C_{13}H_{20}NO_2S$ $(M\text{-}pTolSO_2+H)^+$: 254.1215. Found: 254.1210. Calcd. for $C_{14}H_{23}NNaO_3S$ $(M\text{-}pTolSO_2+Na+MeO^-)^+$: 308.1290 Found: 308.1283.

***N*-[Cyclopentyl(tosyl)methyl]-4-methylbenzenesulfonamide (15).** Following the typical procedure A.3, the reaction of cyclopentanecarboxaldehyde (0.50 mL, 4.54 mmol) with *p*-toluenesulfonamide (0.79 g, 4.54 mmol) and $TolSO_2Na$ (1.0 g, 5.45 mmol) afforded **15** as a white solid; yield: 1.48 g (80%); m.p: 111-112 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.69 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.19 (d, *J* = 10.6 Hz, 1H), 4.73 (dd, *J* = 10.3 Hz, *J* = 5.1 Hz, 1H), 2.67 – 2.64 (m, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 1.89 – 1.85 (m, 2H), 1.57 – 1.54 (m, 4H), 1.30 – 1.26 (m, 2H).**^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm):145.0, 143.5, 138.1, 133.8, 129,7, 129.5, 129.4, 126.7, 38.9, 30.2, 27.9, 24.9, 24.7, 21.8, 21.5. **HRMS-ESI** calcd. for $C_{13}H_{18}NO_2S$ (M-p$TolSO_2$+H)$^+$: 252.1052. Found: 252.1058. Calcd. for $C_{14}H_{21}NNaO_3S$ (M-p$TolSO_2$+Na+MeO^-)$^+$: 306.1140. Found: 306.1140. **Elemental analysis**: calcd. for $C_{20}H_{25}NO_4S_2$: C, 58.94; H, 6.18; N, 3.44; S, 15.74. Found: C, 58.56; H; 6.11; N, 3.38; S, 15.50.

***N*-[Cyclohexyl(tosyl)methyl]-4-methylbenzenesulfonamide (16).** Following the typical procedure A.3, the reaction of cyclohexanecarboxaldehyde (0.93 mL, 10.00 mmol) with *p*-toluenesulfonamide (1.71 g, 10.00 mmol) and $TolSO_2Na$ (1.97 g, 12.00 mmol) afforded **16** as a white solid; yield: 3.01 g (71%); m.p = 101-103 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.69 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 5.28 (d, *J* = 10.6 Hz, 1H), 4.50 (dd, J = 10.7 Hz, *J* = 2.8 Hz, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 2.43 – 2.41 (m, 1H), 2.06 – 2.03 (m, 1H), 1.76-1.72 (m, 4H), 1.23 – 1.19 (m, 2H), 1.07 – 1.03 (m, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.0, 143.4, 138.2, 134.2, 129.7, 129.5, 129.3, 126.7, 37.4, 31.0, 27.2, 26.2, 25.7, 25.6, 21.8, 21.6. **HRMS-ESI** calcd. for $C_{14}H_{20}NO_2S$ (M-*p*$TolSO_2$+H)$^+$: 266.1215. Found: 266.1210. Calcd. for $C_{15}H_{23}NNaO_3S$ (M-*p*$TolSO_2$+Na+MeO^-)$^+$: 320.1296; Found: 320.1278.

4-Methyl-*N*-(3-phenyl-1-tosylpropyl)benzenesulfonamide (17). Following the typical procedure A.3, the reaction of hydrocinnamaldehyde (1.46 mL, 10.00 mmol) with *p*-toluenesulfonamide (1.71 g, 10.00 mmol) and $TolSO_2Na$ (1.97 g, 12.00 mmol) afforded **17** as a white solid; yield: 3.91 g (88%); m.p = 127-129 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.60 (d, *J* = 8.3 Hz, 2H), 7,46 (d, *J* = 8.5 Hz, 2H), 7.23-7.15 (m, 7H), 6.96 (d, *J* = 6.7 Hz, 2H), 5.33 (s, 1H), 4.50 (dt, *J* = 10.3 Hz, *J* = 4.1 Hz, 1H), 2.68 – 2.39 (m, 3H), 2.36 (s, 3H), 2.33 (s, 3H), 2.01 – 1.81 (m, 1H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.4, 143.8, 139.8, 137.8, 132.7, 129.8, 129.7, 128.6, 128.4, 126.8, 126.4, 73.2, 31.3, 30.3, 21.8, 21.6. **HRMS-ESI** calcd. for $C_{16}H_{18}NO_2S$ (M-pTolSO_2+H)$^+$: 288.1058. Found: 288.1047. Calcd. for $C_{17}H_{21}NNaO_3S$ (M-pTolSO_2+Na+MeO$^-$)$^+$: 342.1140; Found: 342.1134.

(*E*)-4-Methyl-*N*-(1-tosylhept-4-enyl)benzenesulfonamide (18). Following the typical procedure A.3, the reaction of *trans*-4-hepten-1-al (1.50 mL, 11.37 mmol) with *p*-toluenesulfonamide (1.97 g, 11.37 mmol) and $TolSO_2Na$ (2.48 g, 13.64 mmol) afforded **18** as a white solid; yield: 1.48 g (30%); m.p = 103-105 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.73 (d, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.42-5.39 (m, 1H), 5.23-5.20 (m, 2H), 4.58 (dt, *J* = 9.6 Hz, *J* = 4.1 Hz, 1H), 2.49 (s, 3H), 2.45 (s, 3H), 2.30 – 2.17 (m, 1H), 2.15 – 1.59 (m, 4H), 1.58 – 1.56 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.3, 143.7, 137.9, 133.8, 132.8, 129.8, 129.7, 129.6, 126.8, 126.1, 73.4, 28.7, 23.0, 21.8, 21.5, 20.5, 14.1. **HRMS-ESI** calcd. for $C_{14}H_{20}NO_2S$ (M-pTolSO_2+H)$^+$: 266.1215. Found: 266.1215. Calcd. for $C_{15}H_{23}NNaO_3S$ (M-pTolSO_2+Na+MeO$^-$)$^+$: 320.1296; Found: 320.1275.

***N*-[2-(Benzyloxy)-1-tosylethyl]-4-methylbenzenesulfonamide (19).** Following the typical procedure A.3, the reaction of 2-(benzyloxy)acetaldehyde (0.40 mL, 2.85 mmol) with *p*-toluenesulfonamide (0.48 g, 2.85 mmol) and $TolSO_2Na$ (0.56 g, 3.42 mmol) afforded **19** as a white solid; yield: 0.91 g (70%);

m.p = 118-120 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.71 – 7.66 (m, 2H), 7.65 – 7.59 (m, 2H), 7.38 – 7.32 (m, 3H), 7.28 – 7.23 (m, 3H), 7.23 – 7.17 (m, 3H), 5.52 (d, *J* = 10.2Hz, 1H), 4.71 – 4.63 (m, 1H), 4.96 (dt, *J* = 11.8 Hz, *J* = 7.7 Hz, 2H), 4.12 (dd, *J* = 10.8 Hz, *J* = 3.1 Hz, 1H), 3.64 (dd, *J* = 10.7 Hz, *J* = 4.3 Hz, 1H), 2.47 (s, 3H), 2.45 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.3, 143.9, 137.3, 136.6, 133.3, 129.7, 129.6, 129.6, 128.4, 128.0, 127.8, 127.0, 73.7, 72.7, 65.9, 21.7, 21.6. **HRMS-ESI** calcd. for $C_{16}H_{18}NO_3S$ (M-pTolSO$_2$+H)$^+$: 304.1007. Found: 304.1015. Calcd. for $C_{17}H_{21}NNaO_4S$ (M-pTolSO$_2$+Na+MeO$^-$)$^+$: 358.1083. Found: 358.1102.

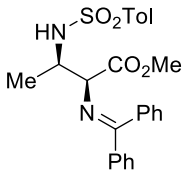
4-Methyl-*N*-(tosylmethyl)benzenesulfonamide (30). Following the typical procedure A.3, the reaction of formaldehyde (0.74 mL, 37% w/w aq. solution, 10.00 mmol) with *p*-toluenesulfonamide (1.71 g, 10.00 mmol) and TolSO$_2$Na (1.97 g, 12.00 mmol) afforded **30** as a white solid; yield: 2.91 g (86%); m.p = 161-162 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.77 (d, *J* = 8.3 Hz, 2H), 7,62 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 5.34 (t, *J* = 7.4 Hz, 1H), 4.37 (d, *J* = 7.1 Hz, 2H), 2.50 (s, 3H). 2.47 (s, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 145.7, 144.2, 136.8, 133.0, 130.0, 129.8, 129.1, 126.8, 63.5, 21.8, 21.6. **HRMS-ESI** calcd. for $C_8H_{10}NO_2S$ (M-pTolSO$_2$+H)$^+$: 184.0426; Found: 184.0433. Calcd. for $C_9H_{13}NNaO_3S$ (M-pTolSO$_2$+Na+MeO$^-$)$^+$: 238.0514; Found: 238.0501. **Elemental analysis**: calcd. for $C_{15}H_{17}NO_4S_2$: C, 53.08; H, 5.05; N, 4.13; S, 18.89. Found: C, 53.32; H; 5.05; N, 4.06; S, 18.64.

A.5.4. Typical procedure for the catalytic asymmetric direct Mannich reaction

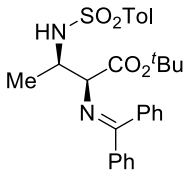
Typical procedure A.4: To a solution of (*R*)-Fesulphos (6.87 mg, 10 mol %) and Cu(CH$_3$CN)$_4$PF$_6$ (5.59 mg, 10 mol %) in dry THF (2.0 mL), under inert atmosphere and the optimum temperature (indicated in each case), were successively added the corresponding glycine derivative (0.15 mmol), Cs$_2$CO$_3$ (0.22 mmol) and the aliphatic α-amido sulfone (0.19 mmol). The reaction mixture was stirred upon consumption of the starting material (TLC monitoring) and filtered through a pad of Celite. After

solvent evaporation, the reaction crude was analyzed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio and then purified by column chromatography on silica gel (eluent indicated for each case). All the products, were isolated as inseparable mixtures of *syn*/*anti* diastereoisomers, which were analyzed by chiral HPLC to determine the *ee*.

Racemic Mannich reaction: In spite of the high diastereo and enantio-selectivities achieved with the Fesulphos ligand, very poor *syn*/*anti* mixtures were obtained following the general procedure using dppf [1,1´-Bis-(diphenylphosphino)-ferrocene] and $Cu(CH_3CN)_4PF_6$ (10 mol%)as the catalyst.

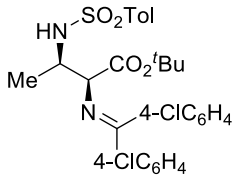
(2*S*,3*R*)-Methyl-2-(diphenylmethyleneamino)-3-(4-methylphenylsulfonamido)-butanoate (3). 

Following the typical procedure A.4, the reaction of methyl 2-[(diphenylmethylene)amino]acetate **2a** (38.0 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosylethyl)benzenesulfonamide **1a** (69.0 mg, 0.19 mmol) in THF (2.0 mL) at rt for 5 h, afforded, after flash column chromatography (*n*-hexane/EtOAc 6:1), *syn*-**3** as a yellow oil; yield: 35.1 mg (52%, *syn*/*anti* = 88:12). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.68 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.53 (m, 2H), 7.39 – 7.32 (m, 4H), 7.30 – 7.24 (m, 2H), 7.22 – 7.16 (m, 2H), 7.03 – 6.91 (m, 2H), 5.56 (d, *J* = 9.0 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.86 (d, *J* = 3.0 Hz, 1H), 3.31 (s, 3H), 2.34 (s, 3H), 1.06 (d, *J* = 6.0 Hz, 3H). ***ee*** = 93 %; $[\alpha]_D^{25}$: -14 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 10/90, flow rate 1.0 mL/min (λ= 254.4 nm), τ_{syn}: 15.7 min (2*R*,3*S*) and 21.5 min (2*S*,3*R*).

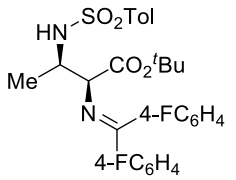
(2*S*,3*R*)-*tert*-Butyl-2-(diphenylmethyleneamino)-3-(4-methylphenylsulfonamido)-butanoate (4). 

Following the typical procedure A.4, the reaction of methyl *tert*-butyl 2-(diphenylmethyleneamino)acetate **2b** (44.3 mg, 0.15 mmol) with **1a** (68.9 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 17 h, afforded, after flash chromatography (*n*-hexane/EtOAc 6:1), *syn*-**4** as a yellow oil; yield: 29.5 mg (40%, *syn*/*anti* = 96:4). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.69 (d, *J* = 8.1 Hz, 2H),

7.58 – 7.52 (m, 2H), 7.36 – 7.32 (m, 4H), 7.31 – 7.26 (m, 2H), 7.20 – 7.14 (m, 2H), 7.04 – 6.96 (m, 2H), 5.51 (d, *J* = 9.2 Hz, 1H), 3.99 – 3.87 (m, 1H), 3.75 (d, *J* = 2.2 Hz, 1H), 2.33 (s, 3H), 1.27 (s, 9H), 0.98 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 172.3, 168.9, 142.8, 139.2, 138.9, 136.2, 130.7, 129.5, 128.8(2), 128.8(0), 128.6, 128.1, 127.4, 126.9, 82.0, 69.3, 52.1, 27.8, 21.5, 19.6. ***ee*** = 97%; **$[\alpha]_D^{25}$**: -17 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 4/96, flow rate 1.0 mL/min (λ= 254.4 nm), τ_{syn}: 21.1 min (2*R*,3*S*) and 33.6 min (2*S*,3*R*).

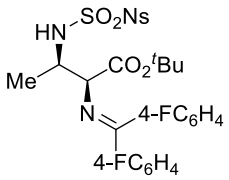
(2*S*,3*R*)-*tert*-Butyl-2-{[bis(4-chlorophenyl)methylene]amino}-3-(4-methylphenyl-sulfonamido)butanoate (5). 

Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-chlorophenyl)methyleneamino]acetate **2c** (54.6 mg, 0.15 mmol) with **1a** (68.9 mg, 0.19 mmol) in THF (2.0 mL), at -20 ºC for 17 h, afforded, after flash chromatography (*n*-hexane/EtOAc 6:1), *syn*-**5** as a light yellow solid; yield: 52.2 mg (62%, *syn/anti* = >98:<2)*;* m.p = 197-200 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.68 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.18 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.40 (d, *J* = 3.0 Hz, 1H), 3.97 – 3.83 (m, 1H), 3.70 (d, *J* = 1.0 Hz, 1H), 2.33 (s, 3H), 1.28 (s, 9H), 0.97 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 169.0, 167.4, 142.0, 138.0, 136.2, 136.0, 134.2, 133.0, 129.0, 128.5, 128.1, 127.8, 127.4, 125.9, 81.4, 68.5, 51.0, 26.8, 20.5, 18.3. ***ee*** = 98%; **$[\alpha]_D^{25}$**: -17 (*c* = 0.6; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 5/95, flow rate 0.7 mL/min (λ= 254.4 nm), τ_{syn}: 26.7 min (2*R*,3*S*) and 72.7 min (2*S*,3*R*).

(2*S*,3*R*)-*tert*-Butyl-2-[bis(4-fluorophenyl)methyleneamino]-3-(4-methylphenyl-sulfonamido)butanoate (6). 

Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with **1a** (68.9 mg, 0.19 mmol) in THF (2.0 mL), at -20 ºC for 17 h, afforded, after flash chromatography

(*n*-hexane/EtOAc 6:1), *syn*-**6** as a light yellow solid; yield: 58.2 mg (74%, *syn*/*anti* = >98:<2); m.p = 163–164 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.67 (d, *J* = 8.3 Hz, 2H), 7.56 – 7.48 (m, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.06 – 6.90 (m, 6H), 5.42 (d, *J* = 9.4 Hz, 1H), 3.97 – 3.84 (m, 1H), 3.71 (d, *J* = 3.0 Hz, 1H), 2.33 (s, 3H), 1.28 (s, 9H), 0.97 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.2, 168.6, 164.5 (d, $^{1}J_{C\text{-}F}$ = 250.5 Hz), 162.8 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 143.0, 139.0, 135.05 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 131.7 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 129.5, 129.4 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 126.9, 115.92 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 115.2 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 82.3, 69.4, 52.0, 27.8, 21.5, 19.4. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.3, -109.4. **HRMS-ESI** calcd. for $C_{28}H_{31}N_2O_4F_2$ $(M+H)^+$: calculated $C_{28}H_{31}N_2O_4F_2S$: 529.1967 Found: 529.1952. ***ee*** = >99 %; **$[\alpha]_D^{25}$**: -35 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 4/96, flow rate 1.0 mL/min (λ= 254.4 nm), τ_{syn}: 19.8 min (2*R*,3*S)* and 50.1 min (2*S*,3*R*).

(2*S*,3*R*)-*tert*-Butyl-2-{[bis(4-fluorophenyl)methylene]amino}-3-(4-nitrophenyl-sulfonamido)butanoate (8). 

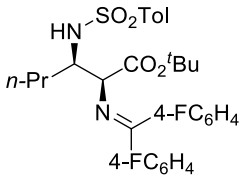
Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with 4-nitro-*N*-(1-tosylethyl)benzenesulfonamide **1b** (75.0 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 17 h, afforded, after flash chromatography (*n*-hexane/EtOAc 7:1), *syn*-**8** as a light yellow oil; yield: 26.7 mg (32%, *syn*/*anti* = >98:<2). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.27 – 8.21 (m, 2H), 8.06 – 7.97 (m, 2H), 7.56 – 7.47 (m, 2H), 7.11 – 6.91 (m, 6H), 5.73 (d, *J* = 9.1 Hz, 1H), 4.09 – 3.94 (m, 1H), 3.71 (d, *J* = 2.6 Hz, 1H), 1.25 (s, 9H), 1.03-0.99 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.8, 168.4, 164.6 (d, $^{1}J_{C\text{-}F}$ = 251.2 Hz), 162.8 (d, $^{1}J_{C\text{-}F}$ = 246.7 Hz), 149.8, 147.8, 134.84 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 131.6 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 129.3 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz), 128.1, 124.2, 116.0 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz), 115.3 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 82.5, 69.2, 52.3, 25.3, 19.9. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -110.9, -109.0. **HRMS-ESI** calcd. for $C_{27}H_{28}N_3O_6F_2S$ $(M+H)^+$: calculated $C_{27}H_{28}N_3O_6F_2S$: 560.1687; Found: 560.1680. ***ee*** = 97%; **$[\alpha]_D^{25}$**: -12 (*c* = 0.3 ; $CHCl_3$).

HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 10/90, flow rate 0.7 mL/min (λ= 254.4 nm), τ $_{syn}$: 23.9 min (2*R*,3*S*), 49.4 (2*S*,3*R*).

(2*S*,3*R*)-*tert*-Butyl-2-{[bis(4-fluorophenyl)methylene]amino}-3-(naphthalene-2-sulfonamido)butanoate (9). Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)-methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with *N*-(1-tosylethyl)naphthalene-2-sulfonamide **1d** (75.9 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 17 h, afforded, after flash chromatography (*n*-hexane/EtOAc 7:1), *syn*-**9** as a colourless oil; yield: 45.5 mg (54%, *syn*/*anti* = >98:<2). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 8.56 (d, *J* = 8.5 Hz, 1H), 8.2 (dd, *J* = 7.3 Hz, *J* = 1.1 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.65 – 7.56 (m, 1H), 7.55 – 7.50 (m, 1H), 7.49 – 7.38 (m, 3H), 7.03 – 6.85 (m, 6H), 5.74 (d, *J* = 9.2 Hz, 1H), 3.85 – 3.80 (m, 1H), 3.61 (d, *J* = 2.8 Hz, 1H), 1.20 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.1, 168.53, 164.5 (d, $^{1}J_{C\text{-}F}$ = 250.5 Hz), 162.8 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 136.62, 135.05 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 134.3, 133.9, 131.6 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.8 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 129.3 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 129.0, 128.9, 128.2, 128.1, 126.7, 124.6, 124.2, 115.8 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 115.1 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 82.4, 69.3, 52.2, 27.8, 18.9. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.3; -109.4. **HRMS-ESI** calcd. for $C_{31}H_{31}N_2O_4F_2$ $(M+H)^+$: 565.1967; Found: 565.1986. ***ee*** = 97%; **$[\alpha]_D^{25}$**: -30 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 5/95, flow rate 0.7 mL/min (λ= 254.4 nm), τ $_{syn}$: 21.6 min (2*R*,3*S*), 44.7 (2*S*,3*R*).

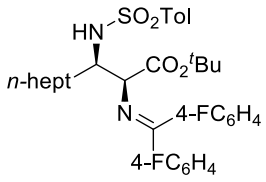
(2*S*,3*R*)-*tert*-Butyl-2-{[bis(4-fluorophenyl)methylene]amino}-3-(4-methylphenyl-sulfonamido)pentanoate (20). Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)-methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosylpropyl)benzenesulfonamide **10** (71.6 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 23 h, afforded, after flash chromatography (*n*-hexane/EtOAc 7:1), *syn*-**20** as a light yellow solid; yield:

72.9 mg (90%, *syn*/*anti* = 99:1); m.p = 151–152 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.71 – 7.64 (m, 2H), 7.55 – 7.47 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.07-6.90 (m, 6H), 5.50 (d, *J* = 9.4 Hz, 1H), 3.85-3.79 (m, 1H), 3.77-3.62 (m, 1H), 2.33 (s, 3H), 1.51 – 1.38 (m, 2H), 1.28 (s, 9H), 0.60 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm) 170.0, 169.1, 164.5 (d, $^{1}J_{C\text{-}F}$ = 249.7 Hz), 162.8 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 142.9, 139.4, 135.1 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 131.8 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.8 (d, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 129.5, 129.4 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 126.8; 115.7 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 115.2 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 82.3, 66.7, 57.9, 27.9, 26.1, 21.4, 10.3. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.2, -109.5. **HRMS-ESI** calcd. for $C_{29}H_{33}N_2O_4F_2S$ $(M+H)^+$: 543.2123; Found: 543.2111. ***ee*** = 99%; **$[\alpha]_D^{25}$**: - 43 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 8/92, flow rate 0.8 mL/min (λ= 254.4 nm), τ_{syn}: 15.0 min (2*R*,3*S*) and 21.4 min (2*S*,3*R*).

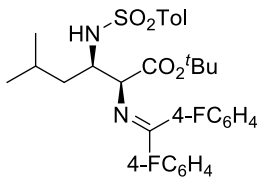
(2*S*,3*R*)-*tert*-Butyl-2-{[bis(4-fluorophenyl)methylene]amino}-3-(4-methylphenyl-sulfonamido)-hexanoate (21). 

Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)-methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosylbutyl)benzenesulfonamide **11** (74.4 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 24 h, afforded, after flash chromatography (*n*-hexane/EtOAct 7:1), *syn*-**21** as a colourless oil; yield: 73.4 mg (88 %, *syn*/*anti* = 96:4). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.71 – 7.63 (m, 2H), 7.55 – 7.46 (m, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.07 – 6.91 (m, 6H), 5.44 (d, *J* = 9.3 Hz, 1H), 3.84 – 3.78 (m, 1H), 3.78 – 3.69 (m, 1H), 2.33 (s, 3H), 1.45 – 1.39 (m, 1H), 1,28 (s, 9H), 1.22 – 1.16 (m, 1H), 0.84 – 0.75 (m, 2H), 0.70 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 169.9, 169.1, 164.5 (d, $^{1}J_{C\text{-}F}$ = 249.7 Hz), 162.8 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 142.9, 139.3, 135.1 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 131.8 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 130.8 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 129.4, 129.3 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 126.7, 115.8 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 115.2 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 82.3, 67.1, 56.1, 35.1, 27.9, 21.4, 18.9, 13.7. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.2, -109.5. **HRMS-ESI** calcd. for $C_{30}H_{35}N_2O_4F_2S$ $(M+H)^+$: 557.2280; Found: 543.2278. ***ee*** = 96%; **$[\alpha]_D^{25}$**: -31 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak IA,

i-PrOH/hexane 10/90, flow rate 0.7 mL/min (λ= 254.4 nm), τ $_{syn}$: 17.02 min (2*S*,3*R*), 26.9 min (2*R*,3*S*).

(2*S*,3*R*)-*tert*-Butyl-2-{[bis(4-fluorophenyl)methylene]amino}-3-(4-methylphenylsulfonamido)decanoate (22). 

Following the typical procedure A.4, the reaction of *tert*-butyl-2-[bis(4-fluorophenyl)methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosyloctyl)benzenesulfonamide **12** (85.3 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 24 h, afforded, after flash chromatography (*n*-hexane/EtOAct 7:1), *syn*-**22** as a light yellow oil; yield: 73.5 mg (80%, *syn*/*anti* = 98:2). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.71 – 7.63 (m, 2H), 7.56 – 7.48 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.06 – 6.89 (m, 6H), 5.48 (d, *J* = 9.6 Hz, 1H), 3.81 (d, *J* = 2.6 Hz, 1H), 3.78 – 3.68 (m, 1H), 2.33 (s, 3H), 1.49 – 1.31 (m, 2H), 1.29 (s, 9H), 1.23 – 1.12 (m, 2H), 1.11-0.98 (m, 7H), 0.91 – 0.83 (m, 1H), 0.78 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 169.9, 169.1, 164.5 (d, $^{1}J_{C\text{-}F}$ = 250.5 Hz), 162.8 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 142.9, 139.3, 134.1 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 131.8 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 129.4, 129.4 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 126.9, 115.8 (d, $^{2}J_{C\text{-}F}$ = 21.9 Hz), 115.2 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 82.3, 67.1, 56.5, 32.9, 31.6, 29.1, 29.0, 27.9, 25.7, 22.6, 21.4, 14.0. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.2, -109.5. **HRMS-ESI** calcd. for $C_{34}H_{43}N_2O_4F_2S$ $(M+H)^+$: 613.2906; Found: 613.2906. ***ee*** = 99%; **$[\alpha]_D^{25}$**: -30 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min (λ= 254.4 nm), τ $_{syn}$: 27.5 min (2*R*,3*S)* and 34.9 min (2*S*,3*R).*

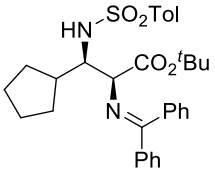
(2*S*,3*R*)-tert-Butyl-2-{[bis(4-fluorophenyl)methylene]amino}-5-methyl-3-(4-methylphenylsulfonamido) hexanoate (23). 

Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(3-methyl-1-tosylbutyl)-benzenesulfonamide **13** (77.1 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 24 h, afforded, after flash chromatography (*n*-hexane/EtOAct

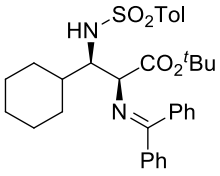
7:1), *syn*-**23** as a light yellow solid; yield: 70.2 mg (80%, *syn*/*anti* = 96:4); m.p = 114-115 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.70 – 7.62 (m, 2H), 7.56 – 7.47 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.06 – 6.89 (m, 6H), 5.42 (d, *J* = 9.4 Hz, 1H), 3.83 – 3.78 (m, 1H), 3.78 – 3.73 (m, 1H), 2.33 (s, 3H), 1.29 (s, 9H), 1.25-1.17 (m, 2H), 0.82-0.77 (m, 1H), 0.73 (d, *J* = 6.2 Hz, 3H), 0.67 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 169.9, 169.1, 164.5 (d, $^{1}J_{C\text{-}F}$ = 250.5 Hz), 162.8 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 142.9, 139.2, 135.1 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 131.8 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.8 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 129.4, 129.3 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 126.9, 115.8 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 115.2 (d, $^{2}J_{C\text{-}F}$ = 21.9 Hz), 82.3, 67.1, 54.6, 41.9, 27.9, 24.4, 22.5, 22.3, 21.4. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.2, -109.5. **HRMS-ESI** calcd. for $C_{31}H_{37}N_2O_4F_2S$ $(M+H)^+$: 571.2436; Found: 571.2457. ***ee*** = 99%; **$[\alpha]_D^{25}$**: -33 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min (λ= 254.4 nm), τ_{syn}: 34.8 min (2*R*,3*S*) and 41.2 min (2*S*,3*R*).

(2*S*,3*R*)-*tert*-Butyl-2-{[bis(4-fluorophenyl)methylene]amino}-4-ethyl-3-(4-methylphenylsulfonamido) hexanoate (24). Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with *N*-(2-ethyl-1-tosylbutyl)-4-methyl-benzenesulfonamide **14** (79.9 mg, 0.19 mmol) in THF (2.0 mL) at rt for 18 h, afforded, after flash chromatography (*n*-hexane/EtOAct 7:1), *syn*-**24** as a light yellow oil; yield: 60.0 mg (70%, *syn*/*anti* = >99:<1). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.72 (d, *J* = 8.1 Hz, 2H), 7.57 – 7.44 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.12 – 6.90 (m, 6H), 5.91 (d, *J* = 8.5 Hz, 1H), 4.11 – 3.98 (m, 1H), 3.86 – 3.75 (m, 1H), 3.09 (s, 3H), 1.42 – 1.29 (m, 1H), 1.26 (s, 9H), 1.23 – 1.04 (m, 2H), 0.92 – 0.76 (m, 2H), 0.72 (t, *J* = 7.0 Hz, 3H), 0.62 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 169.9, 169.6, 164.5 (d, $^{1}J_{C\text{-}F}$ = 249.7 Hz), 162.8 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 142.7, 139.3, 135.0 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 132.1 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 129.4; 129.1 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz), 127.0, 116.2 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 115.6 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 82.2, 65.0, 56.8, 45.5, 27.7, 22.6, 22.1, 21.4, 11.9, 11.6. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.1, -109.4. **HRMS-ESI** calcd. for $C_{32}H_{39}N_2O_4F_2S$ $(M+H)^+$: 585.2593; Found: 585.2567. ***ee*** = 97%;

[α]$_D^{25}$: -44 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak IA, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min (λ= 254.4 nm), τ $_{syn}$: 33.4 min (2*S,*3*R*), 42.2 (2*R,*3*S*).

(2S,3R)-*tert*-Butyl-3-cyclopentyl-2-(diphenylmethyleneamino)-3-(4-methylphenyl-sulfonamido)propanoate (25). 

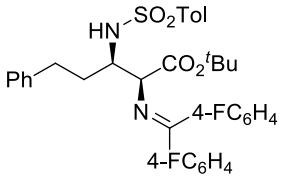
Following the typical procedure A.4, the reaction of *tert*-butyl-2-(diphenylmethylene-amino)acetate **2d** (44.3 mg, 0.15 mmol) and *N*-[cyclopentyl-(tosyl)methyl]-4-methylbenzenesulfonamide **15** (79.5 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 17 h, afforded, after flash chromatography (*n*-hexane/EtOAct 6:1), *syn*-**25** as a white solid; yield: 68.2 mg (83%, *syn*/*anti* = >99:<1*);* m.p = 62-63 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.80 (d, *J* = 8.3 Hz, 2H), 7.68 – 7.59 (m, 2H), 7.48-7.40 (m, 4H), 7.40 – 7.34 (d, *J* = 7.5 Hz, 2H), 7.27 – 7.22 (m, 2H), 7.15 – 7.05 (m, 2H), 5.92 (d, *J* = 8.8 Hz, 1H), 3.98 (s, 1H), 4.05 – 3.90 (m, 1H), 2.41 (s, 3H), 1.98 – 1.80 (m, 1H), 1.60 – 1.45 (m, 3H), 1.45 – 1.35 (m, 2H), 1.39 (s, 9H), 1.24 – 1.01 (m, 2H), 0.95 – 0.86 (m, 1H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.8, 169.3, 142.5, 139.9, 139.0, 130.7, 129.3, 128.9, 128.5, 128.1, 127.4, 126.9, 82.1, 67.9, 60.6, 44.6, 30.1, 29.5, 27.9, 25.11, 24.9, 21.5. **HRMS-ESI** calcd. for $C_{32}H_{39}N_2O_4S$ $(M+H)^+$: 547.2625; Found: 547.2623. ***ee*** = >99 %; **[α]$_D^{25}$**: -18 (*c* = 0.5 ; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 3/97, flow rate 1.0 mL/min (λ= 254.4 nm), τ $_{syn}$: 24.5 min (2*S,*3*R*), 44.6 min (2*R,*3*S*).

(2*S*,3*R*)-*tert*-Butyl-3-cyclohexyl-2-(diphenylmethyleneamino)-3-(4-methylphenyl-sulfonamido)-propanoate (26). 

Following the typical procedure A.4, the reaction of *tert*-butyl 2-(diphenylmethylene-amino)acetate **2d** (44.3 mg, 0.15 mmol) with *N*-[cyclohexyl(tosyl)methyl]-4-methylbenzenesulfonamide **16** (82.2 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 17 h, afforded, after flash chromatography (*n*-hexane/EtOAc 6:1), *syn*-**26** as a white solid; yield: 67.3 mg (80%, *syn*/*anti* = 98:2); m.p = 58–60 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.70 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.39 – 7.25 (m, 4H), 7.36 – 7.18 (m, 2H), 7.18 – 7.11 (m, 2H), 7.05 – 6.90 (m, 2H), 5.90 (d,

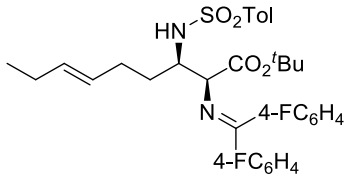
J = 8.7 Hz, 1H), 3.78 (dd, *J* = 1.6 Hz, *J* = 6.72 Hz, 1H), 2.30 (s, 3H), 1.60-1.42 (m, 5H), 1.24 (s, 9H), 1.10 – 0.61 (m, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 171.3, 169.6, 142.6, 139.6, 138.9, 136.6, 130.7, 129.3, 128.9, 128.5, 128.1, 127.2, 126.9, 81.9, 65.7, 60.6, 41.8, 29.7, 29.1, 27.8, 26.3, 26.3, 26.2, 21.4. **HRMS-ESI** calcd. for $C_{33}H_{41}N_2O_4S$ $(M+H)^+$: 561.2781. Found: 561.2783. ***ee*** = 97%; **$[\alpha]_D^{25}$**: -40 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min (λ= 254.4 nm), τ_{syn}: 38.1 min (2*S,*3*R*) and 66.1 min(2*R,*3*S*).

(2*S*,3*R*)-*tert*-Butyl-2-{[bis(4-fluorophenyl)methylene]amino}-3-(4-methylphenyl-sulfonamido)-5-phenylpentanoate (27).



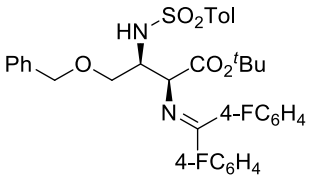
Following the typical procedure A.4, the reaction of *tert*-butyl-2-[bis(4-fluorophenyl)methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) and 4-methyl-*N*-(3-phenyl-1-tosylpropyl)-benzenesulfonamide **17** (86.5 mg, 0.19 mmol) in THF (3.0 mL) at -20 ºC for 18 h, afforded, after flash chromatography (*n*-hexane/EtOAc 7:1), *syn*-**27** as a light yellow solid; yield: 53.2 mg (57%, *syn*/*anti* = 96:4); m.p = 55.4-56.0 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.61 (d, *J* = 7.9 Hz, 2H), 7.53 – 7.44 (m, 2H), 7.21 – 7.12 (m, 4H), 7.11 – 6.85 (m, 9H), 5.54 (d, *J* = 9.4 Hz, 1H), 3.86 (d, *J* = 2.4 Hz, 1H), 3.75 – 3.68 (m, 1H), 2.44 – 2.33 (m, 1H), 2.33 (s, 3H), 2.30 – 2.22 (m, 1H), 1.90 – 1.75 (m, 1H), 1.74 – 1.60 (m, 1H), 1.28 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.1, 169.0, 164.6 (d, $^1J_{C\text{-}F}$ = 250.5 Hz), 162.8 (d, $^1J_{C\text{-}F}$ = 247.5 Hz), 143.0, 140.9, 139.0, 135.1 (d, $^4J_{C\text{-}F}$ = 2.2 Hz), 131.7 (d, $^4J_{C\text{-}F}$ = 3.7 Hz), 130.9 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 129.5, 129.4 (d, $^3J_{C\text{-}F}$ = 7.5 Hz), 128.4, 128.3, 126.9, 126.0, 116.0 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 115.2 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 82.4, 67.0, 55.9, 34.3, 32.0, 27.9, 21.4. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.1, -109.4. **HRMS-ESI** calcd. for $C_{35}H_{37}N_2O_4F_2S$ $(M+H)^+$: 619.2436; Found: 619.2458. ***ee*** = 96%; **$[\alpha]_D^{25}$**: -37 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 15/85, flow rate 0.5 mL/min (λ= 254.4 nm), τ_{syn}: 17.4 min (2*R,*3*S*), 21.4 (2*S,*3*R*).

(2*S*,3*R*)-*tert*-Butyl-2-{[bis(4-fluorophenyl)methylene]amino}-3-(4-methylphenyl-



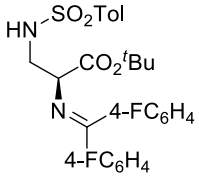
sulfonamido)non-6-enoate (28). Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(1-tosylhept-4-enyl)benzenesulfonamide **18** (85.2 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 20 h, afforded, after flash chromatography (*n*-hexane/EtOAc 7:1), *syn*-**28** as a colourless oil; yield: 70.4 mg (78%, *syn*/*anti* = 90:10). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.71 – 7.64 (m, 2H), 7.57 – 7.48 (m, 2H), 7.22 – 7.14 (m, 2H), 7.09 – 6.92 (m, 6H), 5.49 (d, *J* = 9.4 Hz, 1H), 5.28 – 5.15 (m, 1H), 5.13-4.98 (m, 1H), 3.82 (d, *J* = 2.6 Hz, 1H), 3.81 – 3.72 (m, 1H), 2.33 (s, 3H), 1.80 – 1.60 (m, 4H), 1.47 – 1.33 (m, 2H), 1.29 (s, 9H), 0.78 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.0, 169.0, 164.5 (d, $^{1}J_{C\text{-}F}$ = 249.7 Hz), 162.9 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 142.9, 139.3, 135.1 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 132.6, 131.8 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 129.5, 129.4 (d, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 127.2, 126.9, 115.8 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 115.2 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 82.3, 66.9, 56.0, 32.8, 27.9, 23.5, 21.4, 20.5, 14.2. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.2, -109.5. **HRMS-ESI** calcd. for $C_{33}H_{39}N_2O_4F_2S$ $(M+H)^+$: 597.2593; Found: 597.2601. ***ee*** = 99%; **$[\alpha]_D^{25}$**: -10 (*c* = 0.3 ; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 10/90, flow rate 0.7 mL/min (λ= 254.4 nm), τ_{syn}: 12.0 min (2*R*,3*S*), 16.4 (2*S*,3*R*).

(2*S*,3*R*)-*ter*t-Butyl-4-(benzyloxy)-2-{[bis(4-fluorophenyl)methylene]amino}-3-(4-



methylphenylsulfonamido) butanoate (29). Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) and *N*-[2-(benzyloxy)-1-tosylethyl]-4-methylbenzenesulfonamide **19** (89.62 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 19 h, afforded, after flash chromatography (*n*-hexane/EtOAc 7:1), *syn*-**29** as a light yellow oil; yield: 46.7 mg (50%, *syn*/*anti* = 95:5). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.72 – 7.66 (m, 2H), 7.54 – 7.46 (m, 2H), 7.24 – 7.19 (m, 3H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.08 – 7.02 (m,

2H), 6.98 – 6.84 (m, 6H), 5.59 (d, *J* = 9.1 Hz, 1H), 4.33 – 4.20 (m, 2H), 4.16-4.12 (m, 1H), 4.11 – 4.03 (m, 1H), 3.53 – 3.42 (m, 1H), 3.21 (t, *J* = 9.1 Hz, 1H), 2.31 (s, 3H), 1.21 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.8, 168.8, 164.5 (d, $^{1}J_{C\text{-}F}$ = 249.7 Hz), 162.7 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 143.0, 138.9, 137.6, 135.1 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 131.67 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 9.0 Hz), 129.5 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz), 129.5, 128.3, 127.7, 127.5, 126.9, 115.6 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 115.1 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz), 82.2, 73.1, 69.8, 64.7, 54.8, 27.7, 21.4. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -111.6, -109.5. **HRMS-ESI** calcd. for $C_{35}H_{37}N_2O_5F_2S$ $(M+H)^+$: 635.2385; Found: 635.2389. ***ee*** = 93%; **$[\alpha]_D^{25}$**: -30 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 15/85, flow rate 0.5 mL/min (λ= 254.4 nm), τ_{syn}: 16.2 min (2*R*,3*S*), 36.2 (2*S*,3*R*).

(2*S*)-*tert*-Butyl-2-[bis(4-fluorophenyl)Methyleneamino]-3-(4-methylphenyl-sulfonamido)propanoate (31). 

Following the typical procedure A.4, the reaction of *tert*-butyl 2-[bis(4-fluorophenyl)-methyleneamino]acetate **2d** (49.7 mg, 0.15 mmol) with 4-methyl-*N*-(tosylmethyl)benzenesulfonamide **30** (66.2 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 12 h, afforded, after flash chromatography (*n*-hexane-EtOAc 6:1), *syn*-**31** as a light yellow solid; yield: 61.5 mg (80%); m.p = 59-60 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.61 (d, *J* = 8.3 Hz, 2H), 7.52 –7.43 (m, 2H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.05 (d, *J* = 7.0 Hz, 4H), 6.97 – 6.87 (m , 2H), 4.96 (t, *J* = 6.4 Hz, 1H), 3.98 (t, *J* = 5.8 Hz, 1H), 3.29 (t, *J* = 6.2 Hz, 2H), 2.33 (s, 3H), 1.31 (s, 9H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 170.6, 168.8, 164.5 (d, $^{1}J_{C\text{-}F}$ = 250.5 Hz), 162.9 (d, $^{1}J_{C\text{-}F}$ = 247.5 Hz), 143.4, 137.1, 135.2 (d, $^{4}J_{C\text{-}F}$ = 3.0 Hz), 131.4 (d, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 130.9 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz), 129.7 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz), 129.7, 127.0, 115.8 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz), 115.2 (d, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 82.3, 64.8, 45.6, 27.9, 21.5. **^{19}F NMR (282 MHz, Chloroform-*d*)** δ (ppm): -109.4, -111.3. **HRMS-ESI** calcd. for $C_{27}H_{29}N_2O_4F_2S$ $(M+H)^+$: 515.1810 Found: 515.1804. ***ee*** = 83%; **$[\alpha]_D^{25}$**: -35 (*c* = 1.0; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 4/96, flow rate 1.0 mL/min (λ= 254.4 nm), τ : 30.8 min (2*R)* and 47.2 min (2*S*).

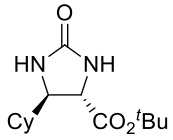
A.5.5. Selective *N*-deprotection of the Mannich adducts: conversion of 26 into the cyclic urea *trans*-32[300]

(2*S*,3*R*)-*tert*-Butyl-2-amino-3-cyclohexyl-3-(4-methylphenylsulfonamido)-propanoate (*syn*-32). To a solution of *syn*-**26** (272.6 mg, 0.48 mmol) in THF (4.0 mL), cooled to 0 ºC, was added a 0.5 M aq. solution of citric acid (2.0 mL). The reaction mixture was warmed up to rt and it was stirred at that temperature for 2 h. Then, it was extracted with Et_2O (3 x 3.0 mL). The combined organic phases were washed with water (3 x 3.0 mL), the aqueous phase was basified with a saturated K_2CO_3 solution and it was extracted with EtOAc (3 x 3.0 mL). The combined organic phases were washed with brine (4.0 mL), dried over (Na_2SO_4) and concentrated under reduce pressure to afford s*yn*-**32** as a colourless oil; yield: 175.0 mg (91%). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.66 (d, *J* = 9.0 Hz, 2H), 7.18 (d, *J* = 9.0 Hz, 2H), 5.27 (s, 1H), 3.44-3.36 (m, 1H), 3.33 (d, *J* = 3.0 Hz, 1H), 2.34 (s, 3H), 1.65-1.42 (m, 7H), 1.36 (s, 9H), 1.10 – 0.61 (m, 6H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 172.8, 143.0, 138.7, 129.4, 127.0, 82.2, 60.2, 54.7, 41.4, 29.8, 28.8, 27.9, 26.2, 26.1, 21.5. **HRMS-ESI** calcd. for $C_{20}H_{33}N_2O_4S$ $(M+H)^+$: 397.2155; Found: 397.2152. **$[\alpha]_D^{25}$**: + 51 (*c* = 0.8; $CHCl_3$).

(4*S*,5*R*)-*tert*-Butyl-5-cyclohexyl-2-oxo-1-tosylimidazolidine-4-carboxylate (*trans*-33). To a solution of *syn*-**32** (260.0 mg, 0.65 mmol) in dry CH_2Cl_2 (4.0 mL), under inert atmosphere and cooled to 0 ºC, was added dropwise a solution of triphosgene (486.1 mg, 1.64 mmol). The reaction mixture was stirred at 0 ºC for 1 h before it was allowed to reach rt and stirred for further 2 h at rt. The mixture was concentrated and the residue was purified by flash chromatography (*n*-hexane/EtOAc 2:1, stained with CAN) to afford *trans*-**33** as a light yellow solid; yield: 220.2 mg (80%); m.p = 73.1-75.0 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.79 (d, *J* = 6.0 Hz, 2H), 7.21 (d, *J* = 6.0 Hz, 2H), 5.77 (s, 1H), 4.24-4.20 (m, 1H), 3.70 (d, *J* = 3.0 Hz, 1H), 2.34 (s, 3H), 1.49 – 1.43 (m, 6H), 1.33 (s, 9H), 1.10 – 0.70 (m, 5H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 169.7, 155.2, 144.6, 136.2, 129.4,

127.9, 83.14, 64.7, 53.0, 41.6, 28.4, 27.8, 26.2, 25.9, 25.5, 25.3, 21.6. **HRMS-ESI** calcd. for $C_{21}H_{31}N_2O_5S$ $(M+H)^+$: 423.1948; Found: 423.1939. Calcd. for $C_{21}H_{30}N_2NaO_5S$ $(M+Na)^+$: calculated: 445.1767; Found: 445.1762. **$[\alpha]_D^{25}$**: + 44 (*c* = 0.7; $CHCl_3$).

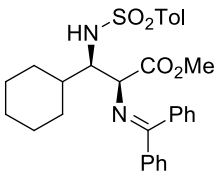
(4*S*,5*R*)-*tert*-Butyl-5-cyclohexyl-2-oxoimidazolidine-4-carboxylate (*trans*-34). To



a solution of *trans*-**33** (45.0 mg, 0.11 mmol) in MeOH (5.0 mL) were added Mg turnings (52.0 mg, 2.13 mmol) and the reaction mixture was stirred under sonication at rt for 1 h. After that time, the Mg was dissolved and the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated and it was dissolved in DCM (2.0 mL), then it was successively washed with a saturated aq. solution of K_2CO_3 (3 x 2.0 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to dryness. The residue was purified by flash chromatography (*n*-hexane/EtOAc 1:2, stained with ninhydrin) to afford *trans*-**34** as light brown solid; yield: 23.9 mg (84%); m.p = 156.1-157.8 ºC. **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 5.48 (s, 1H), 4.98 (s, 1H), 3.82 (d, *J* = 3.0 Hz, 1H), 3.56 – 3.49 (m, 1H), 1.76 – 1.55 (m, 6H), 1.41 (s, 9H), 1.22 – 1.06 (m, 5H). **^{13}C NMR (75 MHz, Chloroform-*d*)** δ (ppm): 169.9, 161.2, 81.5, 59.7, 56.6, 41.8, 27.6, 27.1, 26.9, 25.3, 24.8, 24.7. **HRMS-ESI** calcd. for $C_{14}H_{25}N_2O_3$ $(M+H)^+$: 269.1859; Found: 269.1870. Calcd. for $C_{14}H_{24}N_2NaO_3$ $(M+Na)^+$: 291.1679; Found: 291.1668. Calcd. for $(2M+Na)^+$: 559.3472; Found: 559.3510. **$[\alpha]_D^{25}$**: +38 (*c* = 1.0; $CHCl_3$).

A.5.6. Determination of the absolute and relative configuration of the Mannich adducts: preparation of compound 26´[276]

(2S,3R)-Methyl-3-cyclohexyl-2-(diphenylmethyleneamino)-3-(4-methylphenyl-



sulfonamido)-propanoate (26´). Following the general procedure, the reaction of 2-[(diphenylmethylene)amino]acetate **1a** (38.0 mg, 0.15 mmol) (44.3 mg, 0.15 mmol) with *N*-[cyclohexyl(tosyl)methyl]-4-methylbenzenesulfonamide **15** (82.2 mg, 0.19 mmol) in THF (2.0 mL) at -20 ºC for 24 h,

afforded, after flash chromatography (*n*-hexane-EtOAc 6:1), *syn*-**26´** as a yellow oil, yield: 50.5 mg (65%, *syn/anti* = 90:10). **^{1}H NMR (300 MHz, Chloroform-*d*)** δ (ppm): 7.68 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 7.1 Hz, 2H), 7.40 – 7.25 (m, 4H), 7.21 – 7.14 (m, 2H), 7.01 – 6.90 (m, 2H), 5.89 (d, *J* = 9.0 Hz, 1H), 4.05 – 3.98 (m, 1H), 3.68 (t, *J* = 7.9 Hz, 1H), 3.17 (s, 3H); 2.31 (s, 3H), 1.64 – 1.43 (m, 4H), 1.37 – 1.22 (m, 2H), 1.10 – 0.90 (m, 3H), 0.85-0.69 (m, 2H). **HRMS-ESI** calcd. for $C_{30}H_{35}N_2O_4S$ $(M+H)^+$: 519.2312. Found: 519.2323. ***ee*** = 95%; **$[\alpha]_D^{25}$**: -38 (*c* = 0.9; $CHCl_3$). HPLC: Daicel Chiralpak AD, *i*-PrOH/hexane 3/97, flow rate 0.7 mL/min (λ= 254.4 nm), τ_{syn}: 52.9 min (2*S,*3*R*) and 60.3 min(2*R,*3*S*).[306]

[306] Relative and absolute configuration was determined by comparison with ^{1}H NMR spectrum and optical rotation from the literature. {lit. $[\alpha]_D^{25}$ = -39 (*c* = 1.0, $CHCl_3$)}.

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ANNEX II

Publications

1) ***Catalytic asymmetric Mannich reaction of glycine Schiff bases with α-amido sulfones as precursors of aliphatic imines***

E. Hernando, R. Gómez Arrayás and J. C. Carretero

Chem. Commun. **2012**, *48*, 9622-9624.

Highlighted: a) Synfacts, **2013**, *9(1)*, 0077.

b) Spotlight 424, Synlett. **2013**, *24*, 0529.

2) ***Copper-catalyzed mild nitration of protected anilines***

E. Hernando, R. R. Castillo, N. Rodríguez, R. Gómez Arrayás and J. C. Carretero

Chem. Eur. J. **2014**, *20*, 13854-13859.

Highlighted: a) Frontispiece (Hot Paper).

b) *ChemInform. Abstract*, **2015**, *15*, 46.

3) ***Palladium-catalyzed γ-C(sp^3)–H carbonylative cyclization of α-amino acid derivatives***

E. Hernando, I. Alonso, N. Rodríguez, R. Gómez Arrayás and J. C. Carretero

Angew. Chem. Int. Ed. (manuscript in preparation).